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A GUIDE

TO THE

CLINICAL EXAMINATION

OF

THE BLOOD

FOR DIAGNOSTIC PURPOSES

BY

RICHARD C. CABOT, M.D.

WITH COLORED PLATES AND ENGRAVINGS

Second Edition

NEW YORK
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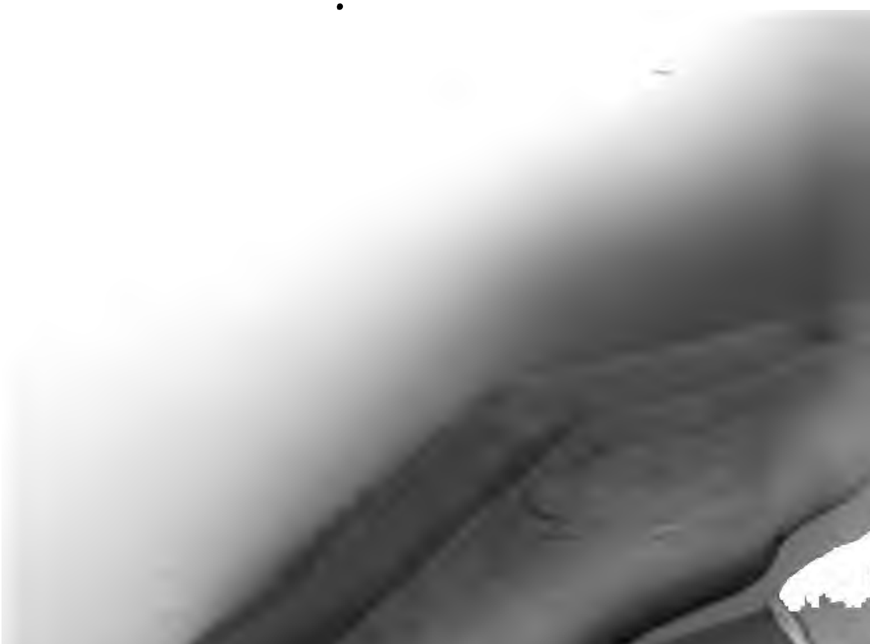
1897



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TO

WILLIAM SIDNEY THAYER, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE IN JOHNS
HOPKINS UNIVERSITY,

IN GRATEFUL RECOGNITION OF THE STANDARD OF THOROUGH
WORK ESTABLISHED BY HIM.

PREFACE.

In order to keep the size of this book within reasonable limits I have omitted all historical account of the steps by which our present knowledge of the different branches of the subject has been built up.

Wherever it has seemed to me that a point was definitely established, I have stated the conclusions generally accepted without special reference to the names of those who worked them out. On the other hand, where our knowledge has seemed to be insufficient I have given some of the names and findings of those who are responsible for the opinions generally current.

Theoretical discussions have been omitted on account of the strictly clinical plan of the book.

The absence of any account of the origin of the blood cells, the chemistry of the blood, coagulation, and many other subjects of great scientific interest is due to the lack of any considerable clinical value in them so far as at present understood.

The body of data referred to from time to time as the "Massachusetts Hospital Blood Counts" consists of nearly four thousand blood examinations, about three thousand of which were made by Drs. Moffitt, Hewes, Joslin, Denny, Franklin White, Capps, and Barney—medical internes of the hospital since 1893. Permission to avail myself of these data was very kindly granted me by the visiting physicians of the hospital. To these I have added about one thousand examinations which I have made both within the hospital and outside. The technique used in all the four thousand examinations was essentially that described in the following pages.

The accumulation of this body of facts and the great mass of foreign hæmatological literature (untranslated) have seemed to me sufficient reasons for the existence of this book—the first of its kind in English, so far as I am aware. Further, it has seemed to me a great pity that there should be no book available con-

taining colored illustrations of stained blood preparations which bear some resemblance to their original, and are not wholly or partly works of the imagination ("diagrammatic").

Funke, of Leipsic, has, I think, been as successful in dealing with the stained blood in the present work as he was with the fresh blood in the beautiful illustrations for W. S. Thayer's monograph on "The Malarial Fevers of Baltimore."

Any one who writes on the blood must be constantly indebted to the following standard text-books: Hayem: "Du Sang," Paris, 1889. v. Limbeck: "Grundriss einer klinischen Pathologie des Blutes," Jena, 1896 (second edition). Grawitz: "Klinische Pathologie des Blutes," Berlin, 1896. Schmaltz: "Pathologie des Blutes," Leipsic, 1896. Rieder: "Beiträge z. Kentniss der Leucocytosis," Leipsic, 1892.

I have usually referred to them in the text as "Hayem," "Rieder," etc., always meaning one of the above works.

The quotations from Schreiber in the text refer to manuscript notes of his lectures in 1896, kindly loaned to me by Dr. Mark W. Richardson.

I am indebted to Dr. F. P. Henry for permission to use the cuts from his recent article on the filaria sanguinis hominis.

December, 1896.

PREFACE TO THE SECOND EDITION.

A NEW chapter on the serum reaction in typhoid fever has been added, and the more obvious mistakes in the text have been corrected. I wish to express my thanks to those who have called my attention to mistakes in the text, especially to Dr. Joseph A. Capps, who has furnished many valuable suggestions.

April, 1897.

190 MARLBOROUGH STREET, BOSTON.

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BOOK I.

INTRODUCTION.

SCOPE AND VALUE OF BLOOD EXAMINATION.

Hæmatology is still so new a study that no confident statement can be made as to the exact limits of its usefulness in the practice of medicine. It has solved some problems where least was hoped from it, and given us disappointingly little help where great expectations had been aroused. We might have expected from it some light on the nature of rheumatism, furunculosis, uræmia, diabetes, but none has come.

On the other hand, who could have hoped that it would help us in the diagnosis of central pneumonia, of deep-seated suppurations and ovarian tumors, etc., or in the prognosis of post-scarlatinal nephritis or of pneumonia?

There are probably not more than five or six diseases in which the blood examination gives us the diagnosis ready-made, but there is a very considerable number of conditions in which the blood examination will help us to make it. Not pathognomonic signs, but links in a chain of evidence are what we are to expect from blood examination. Very often the simple discovery that the blood is normal may be a fact of the greatest value in diagnosis.

On the whole it seems to me that the examination of the blood gives evidence similar in kind and not much inferior in value to that obtained by examination of the urine. Both methods of examination give us (*a*) a ready-made diagnosis in a few diseases; (*b*) side lights on a good many obscure conditions; and (*c*) the frequently great assistance of a negative report. In certain wards of the Massachusetts General Hospital it has been for some years the rule to examine the blood of every patient as a matter of routine at the time of entrance. In a small proportion of cases this gave negative evidence only; in a much larger proportion it materially assisted in the making of a diagnosis.

Improvements in technique have lessened the labor and increased the accuracy of blood examination. The most important facts about the blood of nearly every case can be obtained by a practised observer in fifteen minutes. The experiments of Reinert and others have shown that with due care no error sufficient to mislead judgment need occur.

The blood is the only tissue that we can study easily during the life of the patient. Its relations to all other tissues are such that it is typical of them all in a way that no other tissue is, acting on all and being acted on by all. As yet we have studied chiefly its morphology, and from that single aspect obtained most of the clinically valuable information which we possess about it. But the field of the blood chemistry is in many respects even more promising at the present time, and there seems reason to believe that the study of the blood is still in its infancy and will take a higher place in the future as an aid to diagnosis, prognosis, and treatment.

Like all methods of physical examination it has especial usefulness when we cannot communicate with a patient, either by reason of his unconsciousness, stupidity, or insanity, or because he speaks no widely used language. In such cases the detection of a marked anæmia, a leucocytosis, or a malarial organism may be of the greatest assistance. Malingering is often made more difficult by it, and in the differentiation of organic from functional disease it is often very helpful. There is no febrile disease on which it may not throw light.

The evidence for these and many other aids furnished by the blood examination in clinical work is given in the later chapters of this work.

PART I.

METHODS OF CLINICAL EXAMINATION OF THE BLOOD.

CHAPTER I.

CONFINING ourselves to the clinically available processes by which we can gain information of diagnostic or prognostic value, blood examination at the present time embraces seven processes.

1. Examination of the fresh blood (with or without a warm stage).
2. Counting the red and the white corpuscles.
3. Estimation of the relative *volumes* of corpuscles and plasma by centrifugalizing the blood.
4. Estimation of the amount of coloring matter.
5. Estimation of the specific gravity of the blood.
6. Examination of dried and stained specimens.
7. Bacteriological examination of the blood.

To describe these processes in detail is the purpose of the next chapters.

I. EXAMINATION OF THE FRESH BLOOD.

(*a*) *Obtaining the blood by puncture.* In all the processes about to be described, except the bacteriological examination, the first step is as follows:

Wipe off the lobe of the patient's ear with a damp cloth and then rub it with a dry one. This serves to remove gross dirt and also to make the tissues hyperæmic, so that a slight puncture will draw blood. Attempts to sterilize the skin, or washing it with alcohol and ether, are unnecessary.

Use a three-sided (bayonet-pointed) surgical needle or a small lancet—a sewing needle, even a sharp one, gives more pain and

draws less blood from a given depth of puncture. The needle need not be sterile. In several thousand blood counts made at the Massachusetts General Hospital since 1893 the needles have never been sterilized and no signs of sepsis have been seen in any case.

Possibly this is due in part to the fact that the next step in the process after the puncture has been made is always to wipe away four or five successive drops as they emerge, which serves not only to get the blood flowing freely, but also to wash the ear in its own blood.

The puncture is best made into the lower surface or edge of the lobe, which is steadied with the fingers of the left hand. A very quick stroke gives least pain, the hand rebounding like a piano hammer. If the skin of the lobe is stretched tight with the fingers of the left hand so that no "give" is possible, the quick puncture gives hardly any pain. I have repeatedly taken blood from a sleeping child without waking it. What hurts the patient is the mistaken tenderness that slowly *presses* the needle through the skin. The puncture must be deep enough to make the blood flow freely and without pressure, after it is once started by pressing out a few drops. Blood squeezed out with pressure should never be used for counting, as it is likely to be considerably diluted with fluid pressed out of the neighboring tissues. If the skin is moderately thin and the ear easily made hyperæmic, a puncture one-eighth of an inch deep is sufficient. With thick, bloodless skin it may be necessary to go in one-quarter or one-third of an inch—never more. *Beware of bleeders.* I have seen bleeding from a puncture made for a blood count which could not be checked for three-quarters of an hour. It is always safer to ask after a history of hæmophilia as a matter of routine before taking blood, just as one asks after false teeth before etherizing. If there is a history of hæmophilia, a mere touch of the needle point will give us all the blood we need without embarrassing us with a troublesome hemorrhage.

There is no question, I think, as to the superiority of the ear over the finger for drawing the drop of blood. The ear is decidedly less sensitive than the finger, and a slighter puncture gives us all the blood we need. Moreover, it is often a distinct advantage, especially in children, that the patient cannot watch the puncture of the ear, or the preparations for making it. A

sleeping patient often needs to be roused to get at his finger, while his ear is usually easily accessible above the bed clothes. Again, the absence of any bony prominence against which to press makes us less likely to use too much pressure than if we puncture the finger.

When one is making frequent examinations of the blood of a sensitive person, as in pneumonia, these details are of real importance, and in cases of pernicious anæmia in which the previous attempts to get blood from the finger had been absolute failures, I have found no difficulty in getting it from the ear. In this disease the advantages of the ear over the finger are peculiarly great.

Spreading the Blood.

(*b*) When, after wiping away the first four or five drops, a good-sized drop exudes spontaneously, touch the centre of a perfectly clean cover-glass against the summit of the drop *without touching the skin itself at all*, and drop the cover-glass face downward upon a slide so that the force of the impact will help to spread the drop of blood thinly and evenly between slide and cover. It is recommended by Thayer and others to hold the cover-glass with forceps, but there is no harm in holding it with the fingers, provided we avoid touching either of its surfaces, *i.e.*, hold it always as in Fig. 1.

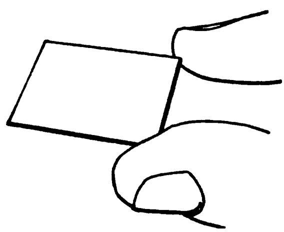


FIG. 1.—Proper Method of Holding a Cover Glass.

Slide and cover must be perfectly clean, else the blood will not spread out in a layer thin enough to avoid the corpuscles overlying each other so that not one of them is clearly seen. Further, as dirt simulates fairly closely some of the pathological appearances for which we are on the lookout, its presence on the slide leads to loss of time or to mistaken conclusions. Cover-glasses, as they come from the shops, are usually coated with a substance not easily to be removed. To get them really clean nothing is so simple as or more effective than soap and water. After several years' use of the method of cleaning usually advised (viz., strong mineral acid, followed by alcohol and then by ether), I have become converted to the use of plain soap and

water as the best and simplest way of cleaning slides or cover-glasses. Rub soap over every part of the glass, wash it off thoroughly with water, and polish it with a clean handkerchief (most towels are apt to leave a scrap of lint on the glass). If slide and cover are perfectly clean, are held as in Fig. 1, and allowed to touch only the summit of the blood drop and not the skin, the blood will spread out properly between them, and no pressure on the cover-glass will be needed to make the layer of corpuscles thin enough. Pressure is undesirable, as it often makes all sorts of artefacts in the preparation and hastens crenation of the red corpuscles. Better results are obtained if slide and cover are *warmed* just before using.

Prevention of Cell-Death.

Slides so prepared are usually best examined with a one-twelfth oil-immersion lens. As a rule they keep long enough for purposes of examination without any further precautions, but if we desire to keep the blood fresh and uncoagulated for a longer period, it is best to exclude air in this way: Paint upon the slide with vaseline, cedar oil, or any gummy substance a hollow square or ring of about the size of the cover-glass, so that when the latter with its drop of blood is put down upon the slide the drop will spread out inside the ring of oil, which seals the margins of the cover-glass to the slide. Specimens so prepared will keep for many hours unchanged, and without crenation or coagulation, if the weather is warm or if the slide be kept in a warm place.

In examining blood suspected of containing malarial parasites it is sometimes useful to put the whole microscope into one of the warming apparatuses devised for the purpose. This is better than any of the various kinds of warm stage in use, but in clinical work there is rarely if ever any need for artificial heating apparatus of any kind, provided the room and the slide are warm.

What Can be Learned from Fresh Blood.

Examination of the fresh blood by the method just described is the best way known for ascertaining the presence or absence of—

1. The Plasmodium malariæ.
2. The Spirochæte of relapsing fever.

3. The Filaria sanguinis hominis.

4. Rouleaux formation among the red cells.

It is also a quick and convenient method of finding out with approximate accuracy:

(*a*) Whether the blood contains an increased amount of fibrin;

(*b*) Whether any considerable anæmia or leucocytosis* is present;

(*c*) Whether or not the amount of hæmoglobin in the red cells is much decreased;

(*d*) Whether the red corpuscles are deformed;

(*e*) Whether the "blood plates" are increased or not.

A practised observer can also make a diagnosis of leukæmia by this method in most cases, but here mistakes may easily occur.

So much can sometimes be learned from a specimen prepared in this very quick and easy way that it should be as much a matter of routine as a urine examination. But in order to get any information from such a preparation we must previously have familiarized ourselves with the appearance of normal blood under such conditions—with the size, shape, color, and refractions of the red cells, white cells, and blood plates and their ratio to one another, and with the great variety of curious phenomena to be seen as a drop of blood gradually dries up between slide and cover. No book can teach this: it must be learned by actual experiment.

Some of the commoner sources of error will be referred to later. Here I will mention only the Brownian movement in the protoplasm of the corpuscles, to be distinguished clearly both from the amœboid movements of the leucocytes or of the malarial parasite and also from the irregular contractions of the dying protoplasm, which give rise to pseudo-amœboid motions in the crenated points of normal red cells or in the irregular projections of corpuscles deformed by disease (*vide infra*).

For a more detailed description of normal red corpuscles, white corpuscles, and blood plates the reader is referred to Part II.

An account of the pathological changes to be observed in the fresh blood will be given in later chapters.

* More accurately it is only the ratio of red to white corpuscles that we can determine, and when the red are very much diminished in number we may be deceived into supposing that the white are increased.

CHAPTER II.

COUNTING THE CORPUSCLES.

Out of the many instruments devised for this purpose that of *Thoma-Zeiss* is so much the most commonly used and most accurate that I shall mention no other. In the use of this instrument there are five steps or stages:

1. Puncturing the ear.
2. Diluting and mixing the blood thus obtained.
3. Adjusting a drop of diluted blood in the counting chamber.
4. Counting the corpuscles.
5. Cleaning the pipette.

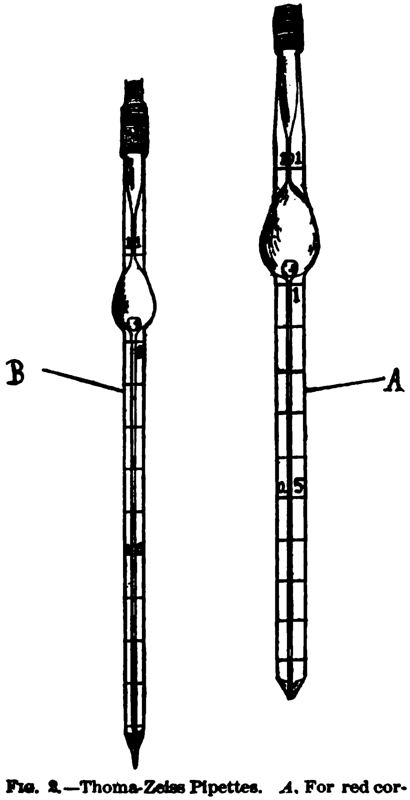


Fig. 2.—Thoma-Zeiss Pipettes. *A*, For red corpuscles; *B*, for white corpuscles.

To count the white corpuscles, a different instrument is often used from that employed for the red.

The technique is nearly the same for both instruments, but for clearness' sake I shall describe them separately. To save time I shall call the small-bore pipette used for red corpuscles (Fig. 2, *A*) the "red counter," and the large-bore pipette (Fig. 2, *B*) the "white counter."

Counting the Red Corpuscles.

(*a*) After puncturing the ear as above described, and as soon as the blood is flowing freely, put the point of the "red counter"

into the drop as it emerges from the ear, and by sucking gently on the rubber tube attached to the other end, draw up blood to the mark 0.5 on the pipette. It needs some practice to stop exactly at the mark, but if we happen to draw the blood up *a little* past the mark 0.5 no considerable error results, provided we draw the column down again to the mark by tapping the point of the pipette on a towel, and provided also that the instrument is perfectly clean and dry. The aim and intention, however, should always be to stop exactly at the mark 0.5, and with a little practice we can do it, except with nervous or delirious patients, and those who carelessly move the head just at the critical moment. With such patients we usually have to content ourselves with drawing the blood a little beyond the mark 0.5 and then drawing it down again to the mark as above described.

Diluting the Blood.

(*b*) The bottle of solution to be used for diluting the blood should be ready uncorked at the bedside. Of the many solutions suggested by various authors none is better than *Gowers'*, the formula for which is as follows:

Sodii sulphat.,	gr. 104
Acid. acetic.,	ʒ i.
Aquæ,	ad ℥ iv.

Toisson's solution is also very useful and stains the white corpuscles so that they can be easily distinguished from the red. Its composition is as follows:

Methyl violet, 5 B.,	.025 gm.
Sod. chlor.,	1.000 "
Sod. sulph.,	8.000 "
Neutral glycerin,	30.000 cm.
Aquæ destill.,	160.000 cm.

We must wait about ten minutes after mixing before the leucocytes are fully stained. Except for this delay, the only difficulty of this solution is that it is rather difficult to clean the pipette after using it. If the white cells are counted with another pipette the staining fluid can be as well dispensed with.

Into a bottle of one of these solutions, ready at the bedside, the point of the pipette is to be plunged as soon as the blood

has been drawn up to the point 0.5 and the outside of the pipette wiped clean of blood. Suction is then exerted through the rubber tube *the instant* the point of the pipette is below the surface of the diluting solution. This suction is continued until the diluted blood has filled the bulb of the pipette and gone past it up to the point marked 101. It is not difficult to stop at this point, provided the pipette is perfectly clean and dry inside. Otherwise it is impossible. Should any mishap occur at this point, the whole process must be begun over again after carefully cleaning and drying the pipette. If no accident happens and the mixture is sucked up to and not past the mark 101, we have diluted the blood with two hundred times its bulk of neutral solution. If, instead of drawing the blood up to the mark 0.5 we draw it as far as the point marked 1, and then dilute as above described, the mixture will be 1 to 100. Some observers habitually use this dilution. The objections to it are: (1) That if the blood is accidentally drawn up too far (*i.e.*, past the mark 1) we cannot draw it down again but must painfully clean and dry out the pipette (see below, p. 16) and repeat the process. (2) If the blood contain approximately the normal number of corpuscles, they will be so crowded when adjusted on the ruled surface of the disc A that it is more difficult to count them. If we use another pipette for the white corpuscles the dilution of 1:100 has no advantage to counterbalance these drawbacks.

While sucking in the diluting solution, it is well to roll the pipette on the long axis with the fingers of the hand which holds it in the diluting fluid. This mixes the blood instantly and prevents any of it from floating on the top of the solution and thereby coming up undiluted into the narrow portion above the bulb of the pipette, where it might possibly escape thorough mixing.*

Next we thoroughly mix the blood and diluting fluid by shaking and rolling the pipette, its ends being closed by the fingers. The little glass ball within the bulb helps this process materially. A minute's brisk rolling and shaking is as good as five minutes', as I have convinced myself by many experiments, and the distribution of the corpuscles throughout the mixture is

* Care must be taken that no saliva finds its way through the rubber tube and into the pipette. Never blow through the rubber tube.

very even, provided there is no delay in proceeding to the next step, viz.:

(c) *Adjusting a Drop of Diluted Blood in the Counting Chamber.* —Remove the rubber tube from the pipette and blow out the portion of diluting solution which *last entered* the pipette, and which consequently has not been thoroughly mixed with the blood in the bulb. Five or six drops should be blown out before any is used for examination. Next put upon the surface of the counter (A, Fig. 3) a drop of such size that when the cover-glass (B)

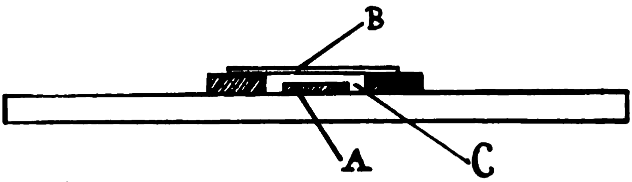


FIG. 3.—Thoma-Zeiss Counting Slide. *A*, Ruled disc; *B*, cover-glass; *C*, moat.

is let down over it the whole of the disc A is covered with the drop without any being spilled into the "moat" (*C*) around it. Just how large such a drop should be can only be learned by practice. It is not literally necessary that exactly the whole disc A should be covered, provided nine-tenths of it is covered, but any spilling over into the "moat" (*C*) entails serious error.

After the cover-glass has been let down upon the drop, we should be able (provided the whole instrument is *clean*) to see concentric rainbow rings between the cover-glass and the body of the instrument. These are known as Newton's rings. A little pressure with a needle on the cover-glass will often bring them out if they do not at once appear, *but they must remain visible* after the pressure is taken off. Otherwise we know that there must be some dirt or dust under the cover-glass preventing its settling exactly into position, and this will cause error in the count, though not a very considerable error in most cases. (To see Newton's rings we should get our eyes near to the level of the counting chamber so that the light from window or lamp is reflected from the surface of the cover-glass.)

If the above conditions are not all fulfilled the instrument should be washed and another drop tried, after shaking the pipette and blowing out a few drops as before.

The cover-glass must be let down as soon as possible after

the drop has been put on the disc A, and before the corpuscles have time to settle. It is best to let it down with a needle as in mounting microscopic specimens.

Counting.

(*d*) After waiting two or three minutes so that the corpuscles may settle thoroughly upon the space ruled off on the disc A,

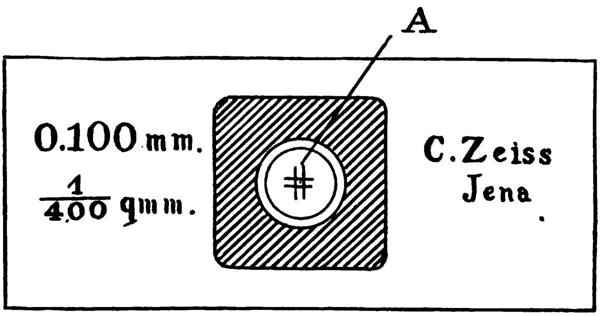


FIG. 4.—Thoma-Zeiss Counting Slide. *A*, Ruled disc.

the counting is begun, using preferably an objective 5 of Leitz or D of Zeiss and a No. 1 or 2 eyepiece.

The ruled space on the surface of the counter (A, Fig. 4). is divided into four hundred squares, every group of sixteen squares being enclosed in double lines to make it easier to know how many squares we have counted (see Fig. 5). Including the squares with double lines we have a group containing thirty-six small squares, a group convenient to count at one time as it just about fills the field of the objective Leitz No. 5, or Zeiss D with a No. 2 eyepiece.

To avoid considerable error we should count the corpuscles in five fields of thirty-six squares each, such as is shown in Fig. 5, taking the fields in various parts of the whole ruled space. The instrument should then be washed and the whole process repeated with a second drop. If the count of the second drop differs widely from that of the first, a third drop should be counted and the average taken of those two which are most nearly alike. Thus at least three hundred and sixty small squares should be counted; with such a number the error is not

over three per cent for practised observers.* In normal blood this means counting about 2,160 corpuscles, as six or seven to a small square is about the normal average when we are using a dilution of 1:200 such as has been described (twelve to fourteen cells per square in a dilution of 1:100).

Among the difficulties encountered in counting is the presence of a few corpuscles on or touching one or more of the lines *bounding* the space to be counted. Shall we count these out or in?

In counting, for instance, a field like that in Fig. 5, what are we to do with the cells which sit astride the lines AA, BB, etc.?

To get round this difficulty, it is best to make it a rule to count *in* all the corpuscles on or touching some two of the boundary lines (*e.g.*, AA and BB) and to take no notice of any cell on or touching the lines CC and DD. In this way the exclusions just balance the inclusions. Of course *all* cells *within* these outer boundary lines are to be counted whatever their position.

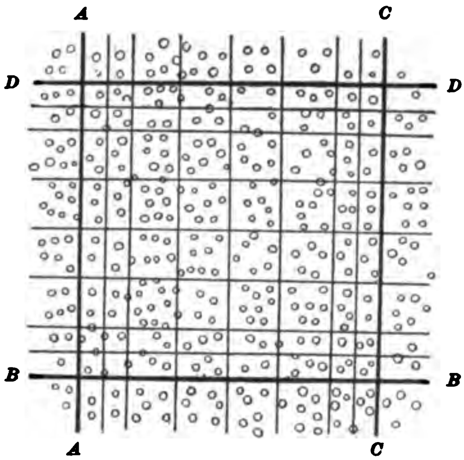


FIG. 5.—Field of Thirty-six Squares on Ruled Disc of Thoma-Zeiss Counter Covered with Normal Blood Diluted Two Hundred Times.

Beyond this the details must be settled by each man for himself. My own habit is to count through the squares in the order indicated by the track of the serpentine arrow in the accompanying Fig. 6, and to count by twos or threes.

A movable stage makes the counting easier, especially for beginners. Either natural or artificial light may be used with a small aperture diaphragm, and if the instruments are clean and the diluting solution fresh and free from sediment,† there is no

* See Reinert's "Zählung der Blutkörperchen," Leipzig, 1891, p. 48 *et seq.*

† Most diluting solutions precipitate or accumulate spores, and need to be frequently renewed.

difficulty in deciding how many cells each square contains, and no extraneous fragments to be excluded. We must distinguish the white corpuscles from the red, not by their size but by their stain if Toisson's solution is used, otherwise by their peculiar shining look when the lens is drawn up so as to put the red cells slightly out of focus. The blood plates are not noticeable and lead to no errors.

When the number of corpuscles in 360 squares has been counted the number is divided by 360 and multiplied by 800,000 (*i.e.*, by 200 to make up for dilution and then by 4,000 because each square is equivalent to $\frac{1}{4000}$ of a cubic millimetre), which gives us the number of corpuscles per cubic millimetre.

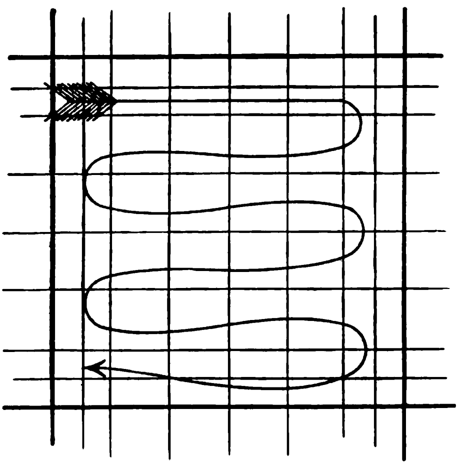


FIG. 6.—The Arrow Indicates the Order in which the Squares are Counted.

These figures need not be committed to memory, for we have marked on the instruments used all the data necessary for the calculation, *i.e.*, the dilution figures on the pipette and the area and depth of a single square on the counting slide.

(*e*) The importance of *cleaning the pipette* as soon as the counting is done is so great that it should be reckoned as one of the regular steps on every count. First water, then alcohol, and lastly ether must be sucked into the pipette and brought into contact with every part of the bulb and tube. After this air must be sucked or pumped through the tube until it is perfectly dry and the glass ball will roll about freely in the bulb without sticking anywhere.

These precautions take but two or three minutes, and if they are omitted and the blood dries in the pipette, it may take several hours' work to get it clean. Further, if it is not thoroughly *dried* after cleaning, the mixing of the blood when it is used next cannot be done accurately.

The first three steps of the above process (*i.e.*, the obtaining, diluting, and mixing of the blood) must be done as swiftly as is compatible with accuracy, but when once the blood is mixed in the pipette it can be kept there indefinitely and counted at leisure. None of the corpuscles are destroyed or lost, and if the bulb is thoroughly rolled and shaken up whenever we are ready to count the blood, no error results from keeping it twenty-four hours or more in the pipette.

It is not necessary, therefore, to carry a microscope to the patient's house or bedside; the pipette and the diluting solution are all that we need to take with us, and when the blood is mixed in the pipette, the latter's ends can be closed with a rubber band and the blood carried home and counted at leisure. The pipette should be kept approximately horizontal during the transit.

Counting the White Corpuscles.

To make a reasonably accurate count of white corpuscles, using the "red counter" and the dilution of 1:100 or 1:200, we need to count an immense number of squares, far more than was necessary in estimating the red cells—in fact, at least ten times the whole ruled space. It is therefore far more convenient and simple to use the "white counter" or large-bore pipette with a diluting solution which renders the red cells invisible and leaves only the white to be counted. Such a solution is the one-third of one-per-cent. solution of glacial acetic acid in water. With this the white corpuscles stand out very clearly and the red can barely be seen at all. The technique is the same as that already described, with the following exceptions:

1. The drop of blood needed is nearly three times as large as that used in the "red counter;" it is about as big as can be made to stay on the ear without rolling off.

2. The bore of the tube being large, it fills and empties more readily. Hence our suction must be gentler, and it is rather harder to stop exactly at the mark 11. For the same reason the diluted blood will run out of the pipette if the latter is not kept nearly horizontal, and the bottle of diluting solution should accordingly be tipped up as we plunge in the point of the pipette, so that the latter is depressed as little and for as short a time as possible before suction begins.

3. Instead of counting separate fields of thirty-six squares each, we should count the whole ruled space and then repeat the process with a second drop. This takes never over fifteen minutes, often not over five, and is very accurate.

The advantages of this pipette are obvious. The only drawbacks are its expense and the need of a somewhat deeper and more painful puncture to get blood enough for it. The technique is not at all difficult.

Counting Both Red and White Cells With the Same Pipette.

We may avoid buying both large-bore and small-bore pipettes in one of the following ways:

1. We can count both red and white corpuscles with the "red counter."

2. We can count both red and white corpuscles with the "white counter."

The reason why we cannot use the "red counter" for counting white cells, unless modified in some way, is that in the whole ruled surface of the counting chamber not more than three or four white corpuscles are to be found in normal blood when diluted two hundred times. If we dilute less, we cannot see the cells distinctly because they are so crowded. If we find, say, three white corpuscles as the number to be used as a basis in calculating the number of white cells in a cubic millimetre, the chance of error is very great, the multiplier being so large (2,000) and the multiplicand so small (3).

To get over this difficulty we may utilize the cells spread over the disc of the counting chamber *outside the ruled space* in one of the following ways:

(*a*) *By measuring the field of the objective used.* The writer's objective, No. 5 of Leitz, has a field of very nearly one-quarter of a square millimetre or one-quarter of the whole ruled space. Four fields of this lens, taken anywhere outside the ruled space, therefore, contain the same number of cells as will cover the whole four hundred small ruled squares, and when we have counted the white cells in a series of four fields of this lens, we have accomplished as much as if we have put a fresh drop upon the counting chamber and counted all the ruled squares over again; the latter process is tedious, the former very quick. Thus it is my practice in some cases to

proceed as follows (see Fig. 7): Supposing the large circle CCCC to represent the surface of the small disc (A, Fig. 3.) in the centre of the counting chamber, and AAAA the ruled squares in the middle of this disc, four microscopic fields are taken in the direction away from the centre indicated by circles and arrows in the figure. Starting, say, to the right of the ruled squares with the left edge of the microscopic field just touching the outer boundary line of the squares, count all the white cells to be seen in the field.

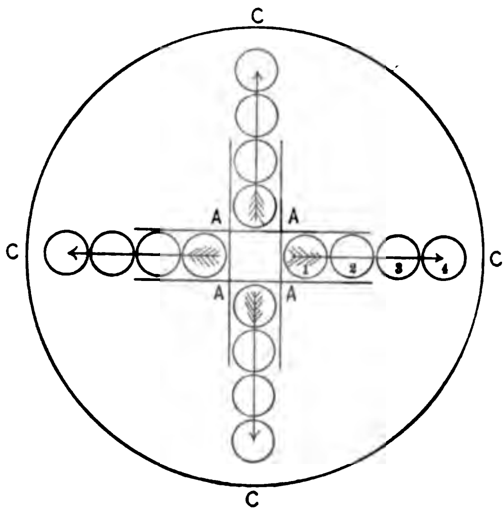


FIG. 7.

Then move along to the right till the corpuscles which were on the extreme right of the first field have gone out of sight to the left. Your field is then in the position of the circle marked 2 (Fig. 7). Count all the white cells in this field and so on for four fields. With my objective, four such fields are almost exactly equal to the whole ruled space AAAA. With other objectives of course the number of fields is different.

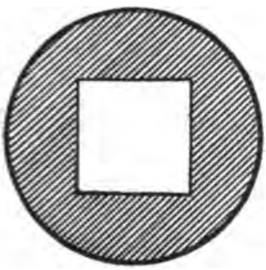


FIG. 8.

When we have counted four fields in each of the four directions indicated by the arrows we have covered as much ground as if we have put four successive drops on the slide after the first one and counted all the ruled squares in each, and we have saved much time and labor.

(*b*) Another and better method of attaining this same end, invented, I think, by Dr. Franklin White, of Boston, is as follows: Cut out of black cardboard a piece of the shape shown in Fig.

8 and of such a size that it will fit into the tube of the eyepiece—the square aperture allowing a space of just one-quarter of a millimetre (one hundred of the ruled squares) to be seen through it with a given objective (say Leitz No. 5). Four fields as seen through such an aperture can then be counted in various parts of the slide outside the ruled space as explained above.

(*c*) For any one living where microscopic ruling on glass can be done at a moderate cost, by far the best way is to have the rest of the disc A (Fig. 4) ruled off in large squares of just a square millimetre each. I have not been able to hear of any one in America who could do such work at a moderate expense.

2. We may use the "white counter" for red corpuscles in the following way: Suck up blood only to the first mark up from the point (*i.e.*, one-fifth of the usual distance) and then Gowers' or Toisson's solution up to the mark 11. This gives a dilution of 1:100, and in anæmic cases, in which the cells are not very numerous, answers well. The same pipette can then be carefully cleaned and used for counting white cells with the acetic acid one-third per cent, and a dilution of 1:10 or 1:20.

Whatever method of counting white corpuscles is adopted, we ought to have at least one hundred corpuscles actually counted to use as the multiplicand of our computation. A single drop from the white counter with a dilution of 1:10 gives us normally about seventy white corpuscles in the four hundred ruled spaces, and by repeating the process with a second drop the result may be made reasonably accurate. This was the method adopted by Rieder* in the immense number of counts made by him.

* "Beiträge zur Kenntniss der Leucocytosis," Leipzig, 1892 (Vogel)

CHAPTER III.

CENTRIFUGALIZING THE BLOOD—HÆMOGLOBIN ESTIMATION —SPECIFIC GRAVITY—STAINED SPECIMENS—BACTERIOLOGICAL EXAMINATIONS.

THE HÆMATOCRIT.

THE hæmatocrit of Hedin, though a comparatively new instrument, has undergone considerable modification and improvement in the last few years and as remodelled and improved by Judson Daland is now coming into use in this country. Its direct and obvious object is simply to ascertain the relative volume or mass of the corpuscles and of the plasma in a drop of blood; but the hope of its advocates has usually been that it would supplant entirely or mostly the long, tedious, and eye-destroying process of counting with the Thoma-Zeiss instrument. Whereas the latter needs sometimes an hour's hard work and eye strain to make an accurate count of red cells, with Daland's centrifugal machine one can get the result in five minutes without any strain on the eyes.

Daland maintains the superior *accuracy* of his instrument in most cases as a further advantage of its use. The estimation of corpuscles depends on the length of the column of corpuscles packed down by centrifugal force at the end of a capillary tube filled with blood and whirled with great rapidity in a horizontal plane. The more corpuscles the longer the column.

Wherever there is much variation in the shape or size of the cells, as in many forms of anæmia, leukæmia, etc., the hæmatocrit is evidently inaccurate, inasmuch as the misshapen, under- or oversized corpuscle will pack down differently from the normal cells, three million undersized cells making a shorter column in the tube than three million healthy ones. This is recognized by the advocates of the instrument, which is accordingly recommended only in those cases in which we know that there are no considerable variations in the size or shape of the red cells. These are usually cases in which no very great anæmia is pres-

ent and in which consequently the labor of counting the large number of corpuscles is greatest. It seems, therefore, as if the hæmatocrit might relieve us of the most irksome part of blood-counting without loss of accuracy.

Against this there is to be said that we do not as yet know how far the elasticity and compressibility of otherwise healthy corpuscles may vary, and how far such a variation may invalidate the standard of tight packing established from other cases. Further, there is known to be a certain amount of variation in the size and volume of a healthy person's corpuscles, both between nations and between members of one nation, and it is yet to be shown whether this variation is sufficient to make the result of the hæmatocrit liable to a greater error than those of

FIG. 9.—Capillary Tube of Hæmatocrit with Rubber Attached.

the Thoma-Zeiss instrument. There is no doubt that the latter is a slower, more tedious instrument; the question is still open whether or not it is the more accurate. Daland reports wide variations between his counts and those of his colleague and between different counts by one observer at different times, using the Thoma-Zeiss instrument, while with the hæmatocrit the variations are but slight.

In testing these results I have made parallel counts of a patient's blood with several of the house physicians at the Massachusetts General Hospital during the last two years and our differences have never exceeded the limit of error laid down by Reinert—namely, two per cent. I think Daland must have been unfortunate in his results.

If, then, the error of the Thoma-Zeiss instrument is, as I believe, not over two per cent under ordinary circumstances and with correct technique, it does not seem likely that the hæmatocrit is a more accurate as well as a simpler and quicker instrument.

To use the Daland hæmatocrit we prick the ear as usual and with the help of a bit of rubber tube attached to one end of the

capillary tube (Fig. 9) suck in enough blood to fill it entirely. Usually we draw in more than enough and it enters the rubber tube as well, but this is no harm. It is nearly impossible to fill the glass tube exactly and no more, inasmuch as the proximal end of it is hidden inside the rubber tube. The commonest

Fig. 10.—Daland's Hæmatocrit. Two capillary tubes in place on the horizontal whirling beam. The instrument is to be fastened to the edge of some solid and bulky piece of furniture by means of the thrumb-screw seen at the bottom of the cut. If not very tightly secured, it will work loose when the handle is revolved rapidly.

mistake at this point is incomplete filling of the capillary tube, as a very large drop is needed to do it.

As soon as it is full, put the finger (greased with vaseline)

tightly over the free end of the glass tube and then, *but not till then*, draw off the rubber tube and adjust the glass as quickly as possible in the place prepared for it on one of the horizontal arms of the whirling machine (Fig. 10). A similar tube (empty) should be put on the other arm of the crosspiece to make the balance true. We must be quick about this, else the blood will coagulate. The handle of the instrument is then revolved at least seventy times a minute for two minutes, at the end of which time (sometimes less) the column of blood cells is packed so tight that no further whirling has any effect on its length. Great care should be taken that the horizontal beam is securely attached to the main part of the instrument, as it is capable of doing serious damage should it come off while whirling nine thousand revolutions a minute, which is the rate usually attained.

It is well to put a little vaseline on the point where the blunt end of the tube rests (*a*, Fig. 10) to prevent any of the blood sticking there when we come to take the tube out and read it.

The capillary tube is marked off into one hundred equal divisions and provided with a magnifier like that on clinical thermometers. Laid on a piece of white paper it is easy to read off the number of divisions occupied by the blood column, although the end of it is often frayed or bevelled in a way that precludes great accuracy. In normal blood the white corpuscles hardly show at all in the tube. They accumulate at the free end of the column of red cells, but unless a leucocytosis is present their presence is indicated, if at all, only by a slight grayish blur at the end of the red column and cannot be accurately measured. This blur is another difficulty in the way of deciding precisely where the end of the red-cell column is.

To estimate the number of red corpuscles from the length of the column, we call each degree of the scale on the tube 100,000 cells, or a little more. Thus if the blood column in the tube ends at about the mark 50 we consider that the blood has rather more than 5,000,000 red corpuscles per cubic millimetre. So far all observers agree on the figures, but as to just how much more or less than 100,000 each degree on the scale is worth there is some variation between different observers. Daland,* in a long series of comparative observations of making blood counts and

* University Med. Mag., November, 1891.

hæmatocrit estimations on the same case, conclude that each degree of the scale on the capillary tube corresponds to 99,390 corpuscles.

The writer in a series of forty observations on healthy persons, in each of which a count of corpuscles with the Thoma-Zeiss instrument and a volumetric estimation with Daland's hæmatocrit was made, found the value of one degree on the glass scale to vary between 105,000 and 123,000 red corpuscles, the average being 112,000.

It certainly seems *a priori* as if variations in the specific gravity of the corpuscles or in the properties of the plasma might make a considerable difference in the number of revolutions needed to reduce the column of corpuscles to its smallest size.

So far as I can learn, the use of this instrument in Europe has been chiefly for the direct information it affords as to the *volume* of the red cells and the amount of respiratory surface in the blood, rather than for the indirect information it may give us as to the *number* of the red cells. It does not seem as yet to be supplanting the Thoma-Zeiss counter.

Its bulk and the noise it makes must for the present, I think, prevent its extensive use outside of hospitals. The noise it makes is a very loud and disagreeable one, and will deter many from using it in private practice.

Hæmoglobin Estimation.

The instrument most used both here and in Europe is that of v. Fleischl. In France Hayem rules supreme in the matter of instruments, as in everything else concerning the blood, and in England Gowers' apparatus is used to a certain extent. Only the v. Fleischl instrument will be described here. The principle of its use is that of directly comparing the tint of the blood with various parts of a strip of colored glass ("*goldpurpur*") whose color shades gradually from a deep red at one end to clear glass at the other. The glass and the blood are brought before the eye side by side and a direct color judgment is attempted.

Use of v. Fleischl's Hæmometer.

(*a*) To use the instrument fill one side of the metallic cell (*a*, Fig. 12) about one-quarter full of distilled water and carry it to the bedside, together with the little capillary pipette (B, Fig. 11) and the needle for puncturing. The capillary pipette must be scrupulously cleaned and dried before use. This is best done by drawing a needle and thread (the latter wet with alcohol and ether) through the eye of the capillary tube. When the drop of blood is flowing freely from the ear, put the end of the little pipette horizontally into the side of the drop, which will at once fill the tube by capillary attraction if the latter is clean and dry. Carefully but quickly wipe away any blood that may be on the outside of the pipette, and make sure that the blood in it is just flush with the surface at each end and does not present a concave or convex surface. Then put it into the water contained in one of the partitions of the metallic cell and rattle it quickly back and forth, so that the water may be forced in first at one end and then at the other. So far in the process we must work very quick to prevent coagulation which in some cases takes place very rapidly.

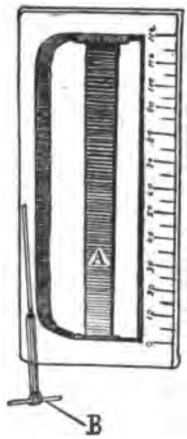


FIG. 11.—*A*, Colored glass; *B*, capillary pipette.

(*b*) After this the cell with the capillary tube still immersed in it may be put in place on the body of the instrument (see Fig. 12) and carried to a room or closet where daylight can be excluded and artificial light used to read the instrument by. Then the expulsion of the blood from the capillary tube may be completed by forcing a few drops of water from a medicine dropper through the capillary pipette and into the compartment where the mixing has been begun. Using the metal handle of the pipette as a stirrer, mix very thoroughly the blood and water in every part of the compartment, looking after the corners especially. Then using a medicine dropper, fill both compartments of the cell to the brim with distilled water, taking care that neither overflows into the other, and adjust the com-

partment containing the clear water so that it comes over the slip of colored glass, while through the compartment containing the blood light thrown upward by the reflector below passes directly to the eye. Turn the thumb screw (see Fig. 12, T) back and forth until the color of the glass is the same as that of the blood, and read off the number on the scale which corresponds

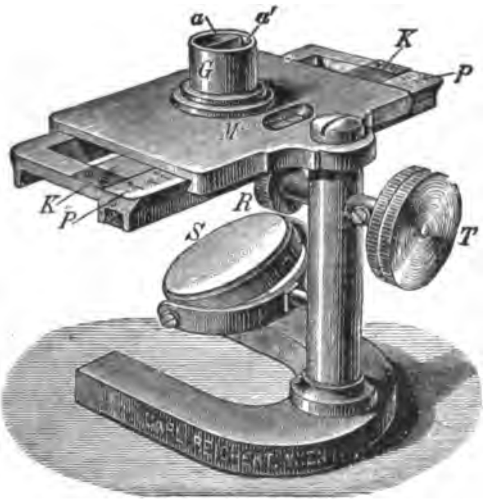


FIG. 12.—v. Fleischl's Hæmometer. *a*, Partition into which blood is put; *a'*, partition into which water is put; *G*, mixing cell; K, K, colored glass slip (see Fig. 11, *A*); *P*, *P*, metal frame on which scale is marked; *R*, *S*, reflector; *T*, screw which moves the frame, *P*, *P*.

to that color. This gives the percentage of hæmoglobin, 100 being the color of normal blood for men and 80–90 for women.

(*c*) *Matching the colors* is not at all easy at best, but may be somewhat aided by observing the following precautions:

1. *Do not stand* (*or sit*) *facing the light, but sideways* (*i.e.*, at A or B, never at C, Fig. 13). For we wish to avoid that the image of one compartment should come on the upper half of the retina and of the other compartment on the lower half, inasmuch as the upper half of the retina is less sensitive to light than the lower and so a less accurate judge of color. By sitting as in Fig. 13, A or B, we get the compartments whose colors we are to match, on the right and left halves of the retina, which are equally sensitive in most persons.

2. *Use as little light as possible,* and always less light for a blood having a low hæmoglobin percentage than for one nearer the normal. Slight color distinctions are abolished if there is any more light than is necessary for simple illumination; too much light dazzles us slightly and so makes us less sensitive in color discrimination.

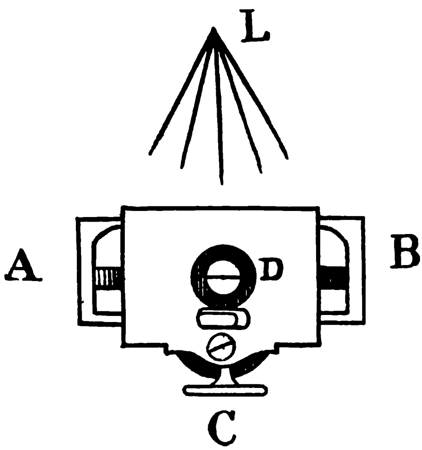


FIG. 13.—*L*, Light; *A* and *B*, right positions for observer; *C*, wrong position for observer; *D*, cell in place.

3. *Roll up a piece of paper (preferably black) into a tube* of such size that it will fit over the metallic cell (D, Fig. 13) and rest on the platform of the instrument. *Looking through this* with one eye we can judge more accurately than without it. Keep the other eye closed.

4. *Use first one eye and then the other, and never look more than a few seconds at a time,* as the eye very quickly gets sufficiently fatigued to lose its finer sensibility. Hence the impression of a first glance is better than a long look.

5. *Move the thumb screw with short, quick turns rather than slowly and gradually,* for sudden color changes affect the retina more than gradual ones. Suppose, for example, we have got as far as to decide that the tint of the diluted blood corresponds to that of glass *somewhere* between the numbers 40 and 60 on the scale. Move the screw suddenly from 40 to 55; the shock of the change will probably convince you that the blood color is lighter than 55. Therefore start this time at 55 and move it suddenly to, say, 45, which may show that 45 is too light. Thus by a series of quick movements of the screw getting shorter and shorter each time (with frequent rests for the eyes) we can probably get it down to a matter of doubt between, say, 42 and 45. Beyond that few persons can go and many can never learn to read without an error of five to ten per cent.

Necessary Errors.

So far as I can see, a certain amount of error is absolutely necessary, inasmuch as the bit of colored glass to be seen at any one time through the aperture of the instrument is not (like the blood) all of one tint, but includes a *variation of twenty per cent in color*, *i.e.*, if the glass appearing at one end of the aperture is opposite 50 on the scale, that seen at the other end of the aperture will either be at 30 or at 70. We have, therefore, to pick out as well as we can the color of the *centre* of the bit of glass showing through the cell and compare the color *at that point* with the color which is evenly distributed throughout the whole of the blood-and-water compartment. This is of course, strictly speaking, impossible. We can no more get hold of and separate out the color of that central point than we can seize and hold fast the present moment. It eludes our grasp.

Many persons are not sensitive enough to colors to attain any reasonable degree of accuracy with the instrument, and there is moreover a very considerable difference between different instruments in respect to the color of the glass slip.* Finally the instrument has been shown to be entirely unreliable for percentages of hæmoglobin under 20.

All these difficulties render the instrument an unsatisfactory one in many ways. Its bulk and expense are also considerable drawbacks.

Is there no other way of getting at the information we desire? None of the other clinically available methods hitherto suggested are any more reliable than v. Fleischl's. But it seems to the writer that in the process next to be described, the specific-gravity estimation, we have a means of getting at the hæmoglobin percentage *indirectly*, which may prove to be in many ways superior to any available *direct* method.

Estimating the Specific Gravity of the Blood.

The simplest and most available method for clinical use is that of Hammerschlag,† a modification of Roy's‡ method.

* Old instruments read lower than those recently manufactured.

† Wien. klin. Wochenschrift, iii., 1,018, 1890.

‡ Proceedings of Physiological Society, 1884.

Chloroform is heavier than blood; benzol is lighter. Mix in a urinometer glass such quantities of the two that the specific gravity taken by an ordinary urinometer is about 1059, *i.e.*, that of normal blood. Puncture the ear, draw a drop of blood into the tube of a Thoma-Zeiss pipette, a small medicine dropper, or any other capillary tube, and blow it out again into the chloroform-benzol mixture. The blood *does not mix at all* with these liquids but floats like a red bead. If it sinks to the bottom add chloroform, if it rises to the top add benzol, until finally the drop remains stationary in the body of the liquid, showing that its specific gravity is just that of the surrounding mixture. Then take the specific gravity of the liquid, as we do of urine, and you have the specific gravity of the drop that floated in it. The following precautions are needed:

1. Have the inside of the urinometer glass perfectly dry and clean; otherwise the drop of blood may cling to it and flatten out against it.

2. It is usually well to have more than one drop of blood in the glass in case any mishap occurs with the first one.

3. Add the chloroform and benzol a few drops at a time, and after each addition stir the whole mixture thoroughly with a glass rod.

4. If we have reason to suppose the blood will be lighter than normal (*i.e.*, if the hæmoglobin is probably low, *vide infra*), it saves time to start with a lighter mixture of chloroform and benzol.

5. Avoid having any *air* within the blood drop. This can generally be seen either in the capillary tube or after the drop is in the mixture. It is safer to take the *middle portion* of the blood drawn into the capillary tube, as both the first and the last portions of the column are more apt to have air in them.

It is better to have a urinometer with a scale running as high as 1070, but this is not essential, for the clinically important specific gravities are *low*, not high.

The importance of the specific gravity of the blood, as hinted above, is not so much for itself, but because it runs parallel to the percentage of hæmoglobin and gives a figure from which the latter can be computed.

The specific gravity of the blood plasma varies very little (except in *dropsy* from any cause), and in the corpuscles them-

selves the variable element is the hæmoglobin.[1] Consequently in most non-dropsical patients the specific gravity of the whole blood varies as directly as the hæmoglobin.

Now, as it is far easier to take the specific gravity accurately than to use the v. Fleischl hæmometer, and as the instruments needed are already in the possession of most physicians and the solutions not expensive, there are evidently great advantages in taking the hæmoglobin in this indirect way. The chloroform-benzol mixture can be filtered and then used over again indefinitely, and the bulk and weight of the urinometer with its glass and the chloroform and benzol bottles, are far less than that of the v. Fleischl instrument.

In dropsical cases we must still use the v. Fleischl instrument. In other conditions I do not see why it should not be supplanted by the cheaper, easier, more accurate, and equally quick method of calculating by specific gravity. To do this one of the following tables may be used. (I. is from Hammerschlag, using the method above described; II. is modified from Schmaltz, "Pathologie des Blutes," etc., Leipsic, 1896, using a direct weighing method.) Apparently a degree of specific gravity means much more at the top of the scale (*i.e.*, 6.6 per cent) than at the bottom ($1\frac{2}{3}$ per cent). These tables are of course not accurate, and further research will be needed to make them so.

I.

Spec. Grav.		Hæmoglobin.
1033–1035	=	25–30 per cent.
1035–1038	=	30–35 "
1038–1040	=	35–40 "
1040–1045	=	40–45 "
1045–1048	=	45–55 "
1048–1050	=	55–65 "
1050–1053	=	65–70 "
1053–1055	=	70–75 "
1055–1057	=	75–85 "
1057–1060	=	85–95 "

II.

Spec. Grav.		Hæmoglobin.
1030	=	20 per cent. ±
1035	=	30 " "
1038	=	35 " "
1041	=	40 " "
1042.5	=	45 " "
1045.5	=	50 " "
1048	=	55 " "
1049	=	60 " "
1051	=	65 " "
1052	=	70 " "
1053.5	=	75 " "
1056	=	80 " "
1057.5	=	90 " "
1059	=	100 " "

STUDY OF THE FINER STRUCTURES OF THE BLOOD.

The study of dried and stained specimens with the help of the aniline dyes gives us much of interest and importance in

[1] Except in dropsy in which the corpuscles themselves may get water-soaked.

regard to the blood. More can be told about a given case by the study of a dried and stained cover-glass specimen than by any other single method.

Preparation of Cover-Glass Specimens.

(*a*) Covers carefully cleaned with soap and water are arranged at the bedside in such position that we can quickly pick them up without touching their surfaces (see Fig. 1). The ear is punctured in the usual way, and one of the cover-glasses touched to the summit of the drop as soon as it emerges. This cover-glass is then let fall upon another in such a way that their corners do not coincide (Fig. 14). If the covers are clean the drop spreads *at once* over their whole surface; as soon as it stops spreading, slide off the top one *without lifting them apart*, but exactly in the plane of their surfaces. Have a gas or alcohol flame at hand and dry instantly if you want to get the very best specimens; but this is not at all necessary for most clinical purposes. The *under* cover-glass is always better spread than the *upper*.

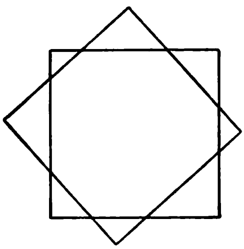


FIG. 14.

(*b*) These covers have now to be *fixed* either by heat or by half an hour's immersion in absolute alcohol and ether (equal parts).

When we wish to study chiefly the changes in the red cells (as in studying the malarial organism, nucleated red corpuscles, degenerative changes, etc.), the alcohol and ether method is preferable. But when, as in the majority of cases, it is the white cells in which our interest centres, the use of heat is very greatly to be preferred.

The method of fixation by alcohol and ether needs little comment, the cover-glasses being simply left in the mixture half an hour or as much longer as is convenient. Half an hour is enough. In most cases we use dry heat, which coagulates the albumin and prevents the hæmoglobin from being washed away. The best way to do this is in a dry heat sterilizer at a temperature of 110–115° C., according to the stain used. The temperature must be gauged very accurately. If we cannot easily get access to such an instrument, we can manage very

well with a strip of copper supported over a Bunsen burner or a small gas or oil stove. The copper plate should be about a foot long and two or three inches wide. Such a plate supported on an iron tripod over a flame gets, after a few minutes, to have a fixed temperature at any given distance from the flame, the heat passing off at the end of the plate as fast as it comes, and so not accumulating. On this plate find the boiling point of water by dropping small drops of water on it, and put the cover-glasses at this point *face downward.* They may be left there for from fifteen minutes to as long as you please; but with the stain which I have used, fifteen minutes' heating gives as good results as a longer period, and excellent specimens can often be made with five minutes' heating.[1] After allowing the specimens to cool they are ready for staining.

Staining.

For all details of structure the Ehrlich tricolor mixture or one of the numerous modifications of it is most convenient. The most useful and easily obtained of these is made by mixing:

Ehrlich-Biondi powder,[2]	gr. xv.
Alcohol (absolute), ...	1 c.c.
Distilled water, ...	6 "

The Ehrlich-Biondi powder is best obtained from G. Grübler & Co., Leipsic, and the same firm supplies leading dealers in this country with the mixture made up ready for use. Several samples of this which I have tested have given excellent results.

Others prefer to make up the tricolor mixture for themselves according to Ehrlich's directions. His latest formula is as follows:

Saturated watery solution of orange G, .	120–135 c.c.
" " " " acid fuchsin, .	80–165 "
" " " " methyl green, .	125 "
Glycerin, ...	100 "
Absolute alcohol, ...	200 "
Distilled water, ...	300 "

[1] If we are in a great hurry, the most important points can generally be made out even if the specimen is simply held in the finger over the flame as hot as can be borne for thirty or forty seconds, and stained the same length of time.

[2] Late specimens of this powder have been unsatisfactory. An absolutely reliable triple-stain from Ehrlich's latest formula can be had of Walter Dodd, apothecary to the Massachusetts General Hospital. A 65-cent bottle will stain several thousand specimens.

I have but little personal experience with this mixture, having generally used the Ehrlich-Biondi stain according to the first receipt given above.

The staining process is remarkably simple. The stain is simply spread over the surface of the cover-glass specimen with a glass rod and washed off again with water after from one to five minutes. The exact time of staining depends (*a*) on the length of time that the specimen has been heated, and (*b*) on the particular specimen of stain. The aniline colors vary so much that it is rare to get two mixtures that stain just alike, even though made upon the same formula.

In a general way the shorter the time we heat the shorter we stain. Thus a specimen hastily prepared by holding it in the fingers over a flame, needs only thirty to sixty seconds staining. Those heated an hour need three to five minutes.

Each observer must work the details out for himself after learning from some "show specimen" how a good stain looks.

After staining and washing in water, the covers are dried between layers of filter paper and mounted in Canada balsam, ready for examination with the one-twelfth oil-immersion lens, with wide open diaphragm.

Differential Counting.

The only procedure in the microscopic examination of such specimens which needs any description is that of making the so-called "differential count" of the leucocytes (*i.e.*, determining what percentage of the leucocytes present belongs to each of the sub-varieties as described on pp. 48–57). To do this accurately we should examine at least one thousand leucocytes—the examination being simply the classification of them under their different sub-varieties. A movable stage is very convenient though not essential for this purpose. With such a stage the technique is simply to start with the lens in, say, the *upper left-hand* corner of the blood film and, by turning the screw of the mechanical stage, move the preparation slowly past the eye until the *upper right-hand* corner is reached. During this process as the cells appear in the field they are checked off and put down under one or another heading. Then move the stage so that the lens is just one field's diameter nearer the *right-hand lower* corner of the preparation, and go back again from right to left, following

the serpentine track indicated above in Fig. 6. To move the lens just one field's diameter we have only to fix the eye on a cell at the extreme edge of the field and then move the stage till that cell disappears out of sight on the *opposite* side of the field. Thus we avoid any chance of counting the same cells twice, and yet are sure not to miss seeing any.

As we go back and forth in this way, we notice chiefly the white cells of course, but yet keep our eyes open for any unusual appearances in the red cells. Usually these move by in a monotonous stream, one looking much like another, but in pathological blood we must always be on the lookout for nucleated red cells, degenerative changes, and variations in size and shape. In malarial cases of course our scrutiny is directed chiefly upon the *red* cells.

If we have not the help of a movable stage we try to do the same thing moving the slide with the fingers. With moderate care there is no danger of counting the same cells twice, but we cannot help missing a good many altogether, so that although accurate the process takes longer.

When leucocytosis is present, at least one thousand leucocytes can be found in a single well-spread seven-eighth-inch cover-glass specimen. In normal blood we may need to go through two to three covers.

Bacteriological Examination.

Blood obtained by the ordinary method of puncture is rarely fit for bacteriological examination. The following is the better way:

Sterilize the skin over the flexor surface of the bend of the elbow, and wash off thoroughly the agents used for sterilization with boiled water or boiled normal salt solution. Have an assistant grasp the upper arm so as to prevent the venous return and distend the large veins at the elbow. Into the most prominent of these plunge a sterilized hollow needle connected with the bulb of a sterilized syringe. All traces of antiseptics must be carefully washed out of the needle and the syringe bulb before using.

When the needle penetrates the wall of the vein the blood usually begins to flow into the bulb of the syringe, and this is

hastened by gently withdrawing the piston until 1–2 c.c. of blood are in the bulb. Then withdraw the needle, press a pad of sterilized gauze over the wound, and expel the blood before it coagulates into a blood-serum culture tube so that it shall run down over the whole surface of the "slant" and collect a little at the bottom. The tubes are then put at once into the thermostat.

In examining for the gonococcus the blood is to be mixed with equal parts of agar-agar (previously melted down so as to be mixable but not hot enough to kill the organisms), and then plated.

The further examination of cultures falls outside the scope of this book.

In the above procedure the only difficulties are: 1. Sometimes it is hard to find a vein and to get the needle into it. 2. Occasionally we get the needle entirely through the vessel into the tisuses on the other side.

If the blood does not flow readily into the bulb one of these two mistakes is usually the cause, but occasionally in those whose vessels are very small or whose circulation is very feeble (as in the moribund) it is very hard to get the requisite amount of blood. Only practice helps us to avoid these difficulties.

The procedure causes hardly more pain than the use of an ordinary subcutaneous injection; the process of sterilization is usually more irksome to the patient than the puncture.

Bleeding is trifling, and within twenty-four hours there is usually no trace of the puncture left. A sterilized dressing with moderate pressure should be applied.

Other Methods of Blood Examination.

It is perhaps worth while briefly to mention some other methods of blood examination of which no account will be given.

1. Determination of the *alkalinity* of the blood. No clinically available method has been devised and the accuracy of any method hitherto described has been doubted by good authorities (v. Noorden, v. Limbeck).

2. *Resistance of the red corpuscles to the influence of distilled water.* As is well known, water breaks up red cells, but if we add a certain amount of alkali, say NaCl, the cells re-

main uninjured. The amount of NaCl which has to be added to prevent the destruction of red cells is from 0.44 to 0.48 per cent. Under certain pathological conditions it needs either more or less of the salt to keep the cells intact, *i.e.*, they possess an increased or diminished power of resistance against the destroying influences of distilled water. The degree of concentration necessary to maintain red corpuscles intact is known as the *isotonic coëfficicnt* of the blood as stated in terms of a given salt; 0.44–0.48 is thus the coefficient of normal blood corpuscles in NaCl.

Possibly this method of examining blood may in the future give us knowledge of clinical value. At present it is not clinically applicable.

The resistance of the blood cells to the influence of electricity, heat, and mechanical pressure has also been investigated in various conditions of health and disease.

3. The rapidity of coagulation varies markedly in different diseases, but no reliable way of measuring it has yet been found.

4. The amount of solids in a given quantity of blood can be determined by weighing a given amount of blood before and after six hours' drying at 65° C. Inasmuch as the hæmoglobin percentage and the specific gravity run practically parallel with the amount of solids this method has no considerable clinical value.

PART II.

PHYSIOLOGY OF THE BLOOD.

CHAPTER IV.

ONLY such portions of our knowledge of blood physiology will be entered upon here as are necessary for an understanding of the small group of pathological changes which can be profitably investigated by clinicians. This limits us for the present to the *morphology* of the blood, its *coloring matter*, and its *density* under physiological conditions.

APPEARANCE OF FRESH NORMAL BLOOD.

A drop of normal blood spread between slide and cover-glass as directed on page 7 and examined immediately with a one-twelfth immersion lens, amazes us first of all by the entire absence of any red color. All we see is a colorless liquid in which masses of very pale greenish-yellow discs are floating or lying.

I. Red Corpuscles.

(*a*) If the blood is spread thickly the blood discs are often arranged in the *form of rouleaux* (Fig. 15). The entire absence of this tendency to rouleaux formation is pathological. It is to be avoided, of course, as far as possible, as it gives us only the thin edges of the corpuscles to look at and covers up much that we need to study. Thin spreading of the blood is therefore important.

(*b*) There is not much variation from the *accurately round shape* of each corpuscle in normal blood, except where one is indented by another. As they are moved about by the currents set in motion by the gradual drying up of the plasma and strike against each other, they bend, double up, or indent each other,

like bags of jelly, but yet always have a strong tendency to return elastically to their round outline when free from pressure. Thus a corpuscle passing through a narrow passage between two leucocytes will be flattened out like a worm; but as soon as it emerges on the other side, it will be as round as before.

(*c*) The central *biconcavity* of the cell, being thinner than the rim, is lighter colored. Just how much lighter should be learned by practice so that we may detect any abnormal *pallor of the corpuscles* due to lack of hæmoglobin. Pallor is to be seen mostly in the centre of the cell, which in extreme cases seems almost transparent. This is not to be confounded with the highly refractile glistening white centres seen as a mark of necrosis as soon as the blood begins to dry up. A fuller description of these appearances is given in the chapter on the malarial organisms, with some forms of which it may be confounded.

(*d*) Slight *variations in size* are present among normal red discs, and here again only practice can teach us where the normal limits end and the pathological begin. Cells may be (pathologically) *all* undersized or *all* oversized, so that a standard of comparison is not always to be looked for in the preparation itself.

(*e*) If we focus carefully on a single red cell we can usually make out a fine, wavy, so-called *molecular motion* in it. This is quite different from the active amœboid movements observed in dying cells, and from the rapid dancing of malarial pigment.

(*f*) The familiar appearance of spines all over the cells usually called "*crenation*" need not be described here (see Fig. 18, p. 72).

But it is the very earliest beginnings of crenation that lead to mistakes, as when only one projection has been developed and that points toward the eye, so that a bright spot in the corpuscles is all we see.

(*g*) Unless we disinfect the skin before puncturing we must be prepared to find in fresh preparations (*a*) oil drops; (*b*) epithelium; (*c*) particles of "dirt;" (*d*) small colorless motile organisms about 1 μ in diameter, which are not at all rare but whose nature is unknown to me.

(*h*) We may make a rough estimate of the *number of red cells* present if we take care to spread the drop of the same thickness each time. The eye gets used to the ordinary look of a well-filled field of corpuscles and notices a look of thinness if any considerable anæmia is present.

(*i*) The *degenerative changes* to be seen in normal blood after long exposure to the air, which can get in between slide and cover, are described in detail later on. In pathological blood we may find these as soon as the blood is drawn.

II. White Cells.

(*a*) *The white or colorless corpuscles* are but little different from the red in color, the latter being so nearly colorless. We first notice them either by their amœboid movements, or because they are not moved by the plasma currents, but stand like a rock round the sides of which the current of red cells is broken. They are slightly larger in most instances than the red cells; but this difference shows less in the fresh specimens where the leucocyte keeps its spherical shape than in the dried and stained preparations, where it is usually somewhat flattened. Their shape is very irregular and their edges often look tattered.

In some leucocytes the amœboid motions are entirely absent. These are the smallest sizes, and in them a single nucleus filling most of the cell can often be seen. They are much more nearly spherical and less irregular than the amœboid cells.

The large amœboid leucocytes are more or less granular, and in certain lights these granules look quite dark and are sometimes mistaken for bits of malarial pigment. This is especially true of the *coarse granular* cells seen occasionally; staining shows these large granules much more distinctly (= eosinophile—see below, p. 51); cells of this type are the most actively amœboid of all.

(*b*) The most important point in connection with the leucocytes is their ratio to the red cells. This is estimated in fresh specimens not by any actual counting but by reference to a standard fixed in the mind by study of normal specimens, and any considerable increase of the white cells would be noticed at once. Naturally we must not judge from any one part of the slide, as the distribution of the leucocytes may be unequal in different parts of it.

III. Blood Plates.

Unless the number of these elements is increased by some pathological influence, we seldom notice them at all in normal blood. This is because we do not work quickly enough in preparing our specimen. Hayem recommends that the cover glass be laid upon the slide before the puncture is made, and as soon as the drop emerges it is allowed to run in between slide and cover by capillary attraction, thus avoiding contact with the air.[1] The blood plates are irregularly shaped, very cohesive elements, about one-half the diameter of a blood disc, usually seen clinging together in masses like zoöglœa. They are colorless and not amœboid and look like *débris.*

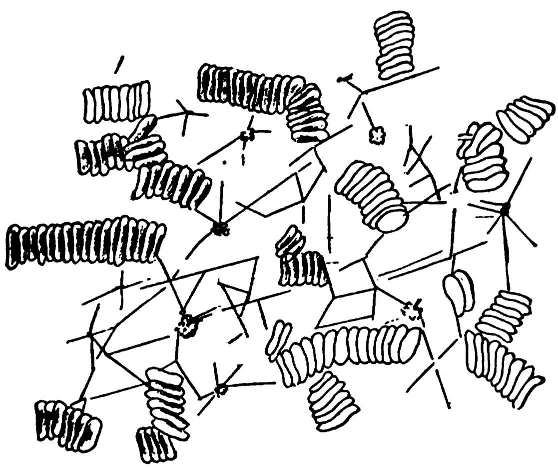


FIG. 15.—Rouleau Formation and Fibrin Network of Normal Blood.

IV. Fibrin Network.

After a specimen of fresh blood has stood for some time exposed to as much air as can creep in between slide and cover-glass, we begin to notice a network of fine straight lines in the spaces between the corpuscles. Here and there these filaments

[1] This is a very satisfactory way if we wish to see the corpuscles as fresh and unspoiled as we can. Put a cover-glass on a slide so that the edge of one is just over the edge of the other, and, holding them in this position with finger and thumb, put their superimposed edges into the side of the drop as it emerges. It will run in between them by capillary attraction.

seem to radiate from a centre where irregular, colorless masses, apparently blood plates, are to be seen (Fig. 15).

No stain is needed to demonstrate these fibrin threads, but a small-aperture diaphragm and very little light makes them plainer. Their only importance is that under certain pathological conditions the fibrin network is very much increased and helps us in the diagnosis (Fig. 16). Hence it is of importance

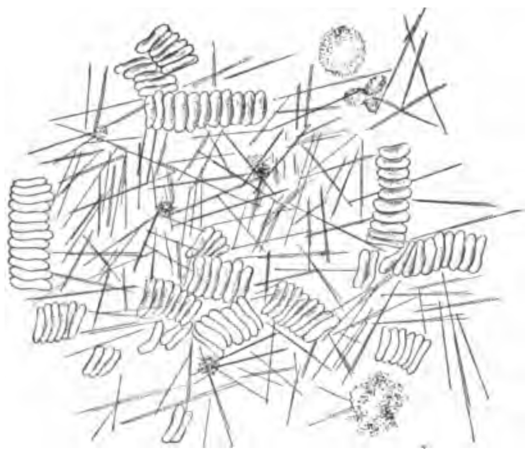


FIG. 16.—Increased Thickness of Fibrin Network.

to be familiar with the ordinary closeness of the network in normal blood as a standard of comparison.

For an account of the conditions of its increase see Chapter IX., page 107.

AVERAGE DIAMETER OF RED CELLS.

The blood under normal conditions shows considerable variations in the size of its corpuscles in the fresh state as well as in stained specimens.[1]

[1] A method of measuring, approximately accurate, and easily applicable in clinical work is the following:

Using a camera lucida, trace on paper the divisions of a fine stage micrometer as seen under a one-twelfth oil immersion lens; such micrometres are usually ruled to one-one-hundreth of a millimetre. Approximate accuracy in our tracing can be obtained if the process is repeated till the divisions marked in successive drawings correspond accurately one with another. Care must be taken that the paper is flat upon the table beside

The following table (v. Limbeck) shows the results of various observers.

	Normal Limits.	Average Diameter.
Welcker	diameter = 4.5–9.5 μ.	7 μ
Valentin		7 μ
Malinin		7.7 μ
Hayem	diameter = 6–8.8 μ.	7.5 μ
Mallassez		7.6 μ
Laache	diameter = 6–9 μ.	8.5 μ
Bizzozero		7.075 μ
Gram	diameter = 6.7–9.3 μ	7.850 μ
	Average =	7.5 μ

These differences depend partly on differences in the method of measuring (wet or dry), and partly on the fact that the age and conditions of nutrition in the persons selected make a difference. In the new-born, and to some extent throughout childhood, the normal limits of variation are wider than in adults (3.3–10.5 μ, Hayem). Sex appears to have no constant influence.

Gram[1] noted that the measurements published by observers living in southern Europe are smaller than those of northern Europe (Italians 7–7.5, Germans 7.8, Norwegians 8.5).

The majority of any individual's red cells are certainly about 7.5 *μ in diameter, and this may accordingly be taken as our standard* (Hayem counts twelve per cent under 6.6 μ, twelve per cent over 8 μ, the rest 7.5 μ).

the microscope, and not raised on a block or otherwise; also that the part of the paper on which we draw should be perpendicularly under the mirror and not off to one side. When a drawing has been made with these precautions, we have only to divide the space between each of the lines in our drawing into ten equal parts, and we have a ruler, each division of which represents 1 μ as seen under a one-twelfth oil immersion lens, with the length of tube of the particular microscope used. To use our μ-ruler we have only to draw with the camera lucida any cell whose size we want to know, using always the same microscope, the same length of tube, and the same lenses, and having the drawing paper (as before) flat on the table and perpendicularly under the mirror. The drawing thus made is measured with the μ-ruler like any other object.

With this method a cell can be measured in a few seconds and with sufficient accuracy (*i.e.*, within 0.5 μ).

[1] Fortschritte der Medicin, 1884.

NORMAL NUMBER OF THE RED CELLS.

1. At the level of the sea and in adult life the normal number of red cells per cubic millimetre is about 5,000,000 for men and 4,500,000 for women. This is not infrequently increased in very vigorous, healthy persons; 6,000,000 is by no means rare among healthy young men, and higher figures are seen occasionally. *Altitude above the sea level* raises the count invariably (see below, page 65).

2. The influence of *menstruation, childbirth, and lactation* is to diminish the red cells temporarily, the amount of the diminution depending not only on the amount of blood lost but on the capacity of the individual organism for blood regeneration. At puberty, when sexual functions are being established, we expect lower counts than after the establishment of the function. Normal pregnancy does not affect the count of red cells.

3. The count of red cells per cubic millimetre is raised by any cause inducing *concentration of the blood*, such as profuse sweating, and is lowered by the temporary dilution of the blood after large draughts of liquid. In these changes, which are always very transient, the hæmoglobin and specific gravity in a given drop are of course increased with the corpuscles.

Vasomotor influences affecting the calibre of the peripheral vessels (hot or cold baths, exercise, etc.) may temporarily concentrate or dilute the blood by affecting the interchange of fluid between the vessels and the surrounding lymph spaces. By these processes the blood in the peripheral vessels may show an increase or diminution in the cellular elements, the hæmoglobin and specific gravity corresponding to the greater or less concentration of the blood at that point (on these points see below page 63).

Hayem noted that in young people especially the number of red cells varied considerably without any notable change in conditions. In adults the oscillations were much smaller.

4. *Influence of Nutrition on the Number of Red Cells.*

A. *After a meal*, especially when considerable liquid is taken, the blood is temporarily diluted and hence the count of red cells

per cubic millimetre is diminished (v. Limbeck; Reinert). This is illustrated by the following case from v. Limbeck.

ADULT, MALE, HEALTHY.

	Red Cells.	White Cells.	Hb
11:15 A.M.	5,530,000	7,660	98 per cent.
12 M. dinner.			
12:15 P.M.	5,320,000	6,166	
1:15 "	5,480,000	8,500	
2:15 "	4,733,000	12,000	
3:15 "	4,872,000	14,000	89 per cent.
4:15 "	4,720,000	10,830	89 "

As the white cells rise (digestive leucocytosis, see below, page 83) the red fall.

Fasting, by concentrating of the blood, temporarily increases the number of red cells (400,000-500,000 increase after twenty-four hours' fast).

B. *General Nutrition.*—Lean, muscular people have on the average more red cells per cubic millimetre than fat people (Leichtenstern, quoted by v. Limbeck), other things being equal.[1]

As above said, fasting (by concentrating the blood) raises the number of red blood cells, so that it is not simply hunger that gives us the *diminution* in red cells commonly found in *poorly nourished people,* but rather the influence of bad hygiene in the slums, etc.

5. *Seasons* and the *time of day* seem to have no influence in themselves. The same is true of *race* and *climate.* The only exception to this is reported in the work of E. Below,[2] who found in yellow fever districts an average count of only 4,700,000 red cells per cubic millimetre and the diameter of the individual cell reduced to 5.9 μ on the average (7.5 μ = normal).

6. *Fatigue.*—Hayem noted a loss of from 500,000 to 1,000,000 red cells per cubic millimetre in the blood of a number of farmers after a hard summer's work, the counts made in September having been compared with those of April and always found to be lower. Whether fatigue is the only cause of this diminution may be doubted.

[1] The influence of stasis in the obese, whose fat loads the surface of the heart, is to cause an apparent increase of red cells (see below, p. 60).

[2] "Deut. Tropenhygiene," Berlin, 1895. O. Coblanz.

7. *Age.*—In the new-born the number of red cells is very high for a few days (7,000,000 to 8,800,000), but falls at the end of seven to ten days (see below, page 86).

In the very old a certain degree of anæmia is, so to speak, physiological; but this, which like the plethora of the new-born is to be referred *not* to the fact of age, but to concomitant influences, is by no means invariable. Schmaltz reports 6,766,000 red cells in a man and of eighty-one and 4,816,000 in a woman of seventy-four.

Normal Number of White Cells.

The figure usually given for adults is 7,500 per cubic millimetre. This varies a good deal, according to the nutrition of the individual (see below, page 81) and also at different times of the day, owing to influences not explained. The influence of digestion will be mentioned later. In animals a slight shock[1] is sufficient materially to affect the count of leucocytes; 5,000 to 10,000 may be called the normal limits. There is, I believe, no evidence to show whether or not mental disturbances (fear, rage, emotion of various kinds) affect their number. Other causes of variation will be discussed under Leucocytosis.

Blood Plates.

The number of blood plates is from 200,000 to 300,000 under normal conditions. They are the chief constituents of white thrombi, and wherever they are diminished (*e.g.*, in hæmophilia, purpura) clotting is apt to be slow. They are increased in leukæmia and in many cases of grave anæmia. In the severer types of many infectious diseases (typhus, erysipelas, malaria) they are diminished, and in malaria they are sometimes wholly absent during the fever. In pneumonia and tuberculosis they are normal or increased. In purpura and hæmophilia they are sometimes much diminished or absent.

The physiological limits of the amount of *hæmoglobin* and of the *specific gravity* have already been mentioned. Under physiological conditions their variations follow those of the count of red cells.

[1] Löwitt: "Studien z. Physiol. und Pathol. d. Blutes," etc., Jena, 1892. Fischer.

CHAPTER V.

FINER STRUCTURE OF THE BLOOD.

I. Appearances of Dried and Stained Specimens.

Cover-glass specimens prepared and stained as above directed give us more information of interest and importance than can be obtained from any other one method of blood examination. Approximate ideas of the quantity of red cells, of white cells, and of hæmoglobin can be formed, parasites and bacteria can be seen, and the whole mass of evidence based on the finer structure of the leucocytes can only be obtained in this way. The appearances of a specimen of normal blood prepared in this way are as follows:

Red Cells.

1. The hæmoglobin stains with the orange G of the tricolor mixture, and in a properly heated specimen the red cells are of a brilliant yellow or pale orange tint. If overheated they have a feebly stained, washed-out look, while if underheated they are more or less brown or gray.

The degree of pallor of the centres corresponding to the amount of hæmoglobin in the corpuscle can be gauged much more accurately with this stain than in the fresh preparations. The color of the edges is not much affected by pathological changes, the centres being the test. But in cases with extreme poverty of hæmoglobin the colored rim may be reduced to a mere shell and the rest may be almost completely colorless. The power to estimate the amount of anæmia in this way can be easily acquired.

An approximate idea of the number of red cells may be formed by any observer who has learned to use a uniform technique in each case and to spread the blood of a standard thickness.

2. Nothing is seen of the fibrin or blood plates, as a rule. In normal cases the plasma does not stain at all.

WHITE CORPUSCLES.

3. The chief purpose and use of the "triple stain" is for distinguishing the varieties of white corpuscles, and the pathological states of the red. About the normal red cells it gives us no information that cannot be obtained as well by various other stains, but our knowledge of normal leucocytes has been immensely enlarged by its use.

In normal blood stained as above directed, we recognize the following varieties of white cells:

(1) *Small lymphoctyes* (see Plate I.). These consist mostly of a round blue nucleus about the size of a red cell, and surrounded by a thin coating of protoplasm, faintly stained or invisible.

The nucleus may be considerably smaller than a red cell, in which case it is almost certain to stain deeply, nearly black. The larger it is the more apt it is to be pale, as if there were a fixed amount of colorable matter which got spread out thin when the nucleus grew larger (see Plate I.).

There is no line to be drawn between this form and that next to be described, namely, the "large lymphocyte" or "large mononuclear cells," which is simply larger and paler.

The small lymphocyte is without much doubt the youngest form of leucocytes seen in the blood—that is, it is the white corpuscle just after it has graduated from the adenoid organs where it is formed. It grows both by increasing its protoplasm and by increasing the size of its nucleus; but the former grows faster than the latter, so that in the so-called "large lymphocyte" the nucleus occupies relatively less of the cell than when it was younger.

In many cases we do not see in the blood all the stages of this growth. Lymphocytes are either "small" (5–10 μ in diameter) or "large" (13–15 μ in diameter) (see Plate I.).

In other cases we find every intermediate size, both of nucleus and of the cells as a whole, and in such cases it is absurd to attempt a division into "large" or "small," though we may be able to say in a general way which size predominates.

(2) The theory that the "*large*" *mononuclear* cells come from the spleen and the small mononuclear from the lymph glands

PLATE I.

FIG. 1.—(*a*) *Polymorphonuclear Neutrophiles.* Note the varieties in size and shape of granules, the irregular staining of the nuclei, the light space around them, their relatively central position in the cell.

(*b*) *Myelocytes.* Note identity of granules with those just described; the even, pale stain of nuclei; their position near the surface (edge) of the cell. The two cells figured indicate the usual variations in the size of the whole cell.

(*c*) *Small Lymphocytes.* In the cell at the left note transparent protoplasm; in the cell next to it note *very* pale pink ring of protoplasm around nucleus which is deeply stained, especially at the periphery. The next cell has an indented nucleus; its protoplasm relatively distinct. The cell on the extreme right shows no protoplasm and is probably necrotic. In all note *absence of granules.*

(*d*) *Large Lymphocytes.* Note pale-stained nuclei and protoplasm, irregularity of outline; indented nucleus in one. Every intermediate stage between these and the "*small*" lymphocytes occurs, and the distinction between them is arbitrary.

(*e*) *Eosinophile.* Note irregular shape, loose connection of granules, their copper color, their uniform and relatively large size, and spherical shape.

(*f*) *Eosinophilic Myelocyte.* Note similarity to (*b*) ordinary myelocytes except as regards granules. Color of granules may be as in (*e*) ordinary eosinophile.

All the above were stained with the Ehrlich-Biondi mixture, and drawn with camera lucida. Oil-immersion objective one-twelfth and ocular No. iii. (Leitz).

FIG. 2.—*Malarial Parasites in Fresh* (*Unstained*) *Blood* (Tertian Forms). *N, N,* normal red corpuscles; 1, red cell containing *hyaline body;* 2, 3, 4, 5, successive stages in the development of the parasite, showing acquisition of pigment; 6, 7, full-grown parasites, the corpuscle no longer visible; 8, beginning of segmentation; 9, segmentation. In 6 and 7 note brownish blur behind the pigment dots. Drawn as in Fig. 1.

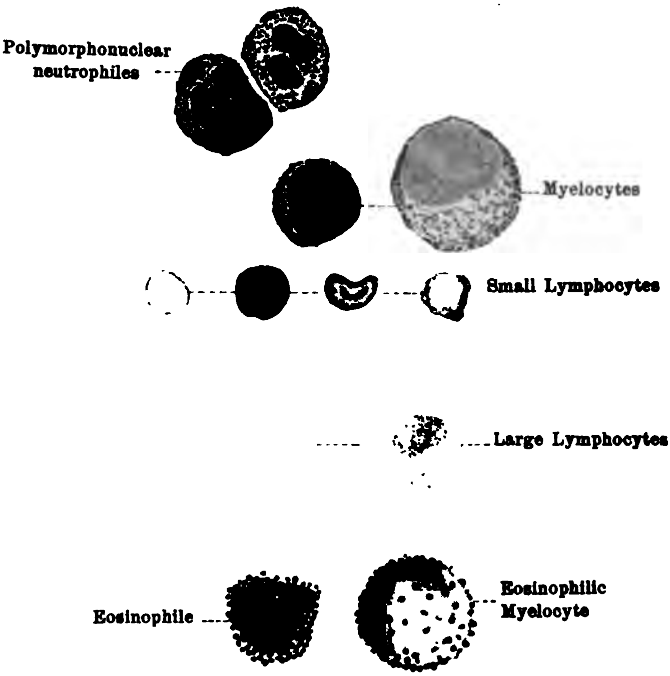
FIG. 3.—*Tertian Parasite Stained with Eosin and Methyl Blue.* The remains of the corpuscle containing the parasite stain pink, the parasite blue, and its pigment black. The stages of growth correspond with the numbers attached. Note in Figs. 1, 2, 3, and 4 the shape of the parasite, shown better than in fresh specimen.

[Owing to a mistake the cells in Fig. 3 are not drawn according to a single scale and their relative sizes must be disregarded.]

Examination of the Blood.

PLATE I.

Fig. 1. **Varieties of Leucocytes.**



The Malarial Organism.

Fig. 2.

Fig. 3.

R. C. Cabot fec.

Lith. Anst. v. E. A. Funke, Leipzig.

has been abandoned by most writers of late years, and it is now generally supposed that all the leucocytes enter the blood (under normal conditions) as small lymphocytes and then grow up, the different forms seen in the circulating blood representing different stages of growth.

The protoplasm of the lymphocytes, as has been said, is always hard to stain. Sometimes it has a faint pinkish tinge, more frequently it is grayish or very light blue, and in some cases it stands out brilliantly transparent and colorless against the faint purplish tinge of the surrounding plasma (see Plate I.).

I have described the lymphocytes so far as "mononuclear," but it is not rare to find even very small ones (6 μ in diameter) whose nucleus has a deep cut in one side or has divided into two parts. I believe it is commoner to find a nucleus in the small forms than in the "large lymphocytes." The inapplicability of the term "small mononuclear cells" or "large mononuclear cells" to this variety of corpuscle is evident. The distinguishing mark is not the single nucleus but the absence of granules.

In the younger and smaller forms of lymphocytes the nucleus, even when dividing, is compact and fills most of the cell. But as it grows older, instead of simply getting larger and paler, the nucleus may begin to bend and branch in the cell and then we get the so-called

(3) "*Transitional forms*," which are no larger than the larger size of lymphocytes, from which they differ only in that they have an indentation in their nucleus—either a narrow cut or a bay so wide that a "horseshoe" nucleus results. This is *the* transitional form according to this nomenclature. There is no reason for calling it so, as all the forms of leucocytes are transitional, but there is some convenience in the name. Like most large lymphocytes it is pale all through—pale in both nucleus and protoplasm—and often escapes notice in hasty examinations. Sometimes its protoplasm is sparsely covered with faint granules.

(4) Next in age come the cells usually known as "polynuclear" but more properly called *polymorphonuclear neutrophiles*. These cells constitute the vast majority of those found in ordinary pus. The main difference between them and those last described is in the possession of granules, when stained by Ehr-

lich's methods. The nucleus stains usually quite deep blue or greenish-blue, and irregularly, *i.e.*, more intensely in some parts than in others. It is very irregular in shape, being twisted about in the body of the cell, possibly in consequence of its amœboid movements. Here and there it may dive down so deeply beneath the surface of the cell that it is hidden under a thick layer of granules, reappearing in another part of the cell so that it seems to be broken in two. Occasionally, no doubt, this is actually the case, but generally there are "underground connections" between the apparently separate pieces of nucleus. Now and then we see a cell (degenerating) where the granules have fallen away, leaving the nucleus like a short, thick snake, very rarely two.

One never sees any two of these cells whose nuclei are of the same shape. Hence the term "polymorphonuclear." The windings and twistings of the nucleus have suggested comparisons to the letters Z, S, E, etc.

The granules which fill the body of the cell and in which the nucleus is embedded stain well only with triple stains like Ehrlich's. Acid stains like eosin, and basic stains like methylene blue, do not bring them out clearly. Hence the term "neutrophilic," which is not strictly accurate; more properly they are oxyphilic.[1] With the Ehrlich-Biondi mixture they stain violet or purple, sometimes pink. They are very small and irregular in shape and size, contrasting with the large, round, "eosinophile" granules (see below). The cells being spherical the granules lie *over* and around the nucleus, not simply *at the side* of it. In their interstices we seem to see a pinkish background of cell substance. These "neutrophilic" granules, which are so small that except with very high powers they look like a diffuse stain, are generally developed only in the adult life of the cell. In normal blood we rarely if ever find them except in cells whose nucleus has reached the polymorphous stage. Occasionally we seem to see *mononuclear neutrophiles*, having a round nucleus

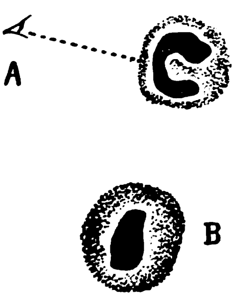


FIG. 17.

[1] Ehrlich's stain is really a differential acid stain and not neutral.

with neutrophilic granules, but careful focussing usually shows that the appearance of a round or rod-shaped nucleus is given by the tight coiling of the ribbon-like nucleus round one of its ends, or else that a horseshoe nucleus is seen from the point of view indicated in Fig. 17. Thus if the eye be at the point A the nucleus will appear of the shape indicated in B.

(5) If the variety of leucocyte last described is to be considered as "adult" or "ripe," the *eosinophiles* will correspond to the old or overripe cell. There are some difficulties in the way of this hypothesis, but it is convenient to adopt it for the present.

The "over-ripe" cell has, like its predecessor, a polymorphous nucleus and granules; but the nucleus is paler and more loosely connected to the granules, and the latter are accurately spherical, of uniform size, and much larger than any seen in the neutrophilic cell. They have strong affinity for acid coloring matters (eosin, acid-fuchsin, etc.), hence their name. In specimens stained with simply eosin or eosin and methyl blue they are very brightly colored pink. With the Ehrlich-Biondi mixture they are more of a copper or burnt-sienna color. Someind ividual granules stain much darker than others in the same cell.

The eosinophiles are the most actively amœboid of all the corpuscles, and it may be for this reason that the different parts of the cell seem so loosely strung together. The granules may be all at one side of the cell and the nucleus on the other, and in cover-glass specimens we very frequently find actual separation of the two, whether or not by the technique of spreading the blood is unimportant, as we find such broken cells much more often among the eosinophiles than among any other variety—which argues a weaker structure.

Sometimes there seem to be two or more distinct and separate nuclei in the cell, no "underground connection" being traceable. The granules are seldom *over* the nucleus as we see it in cover-glass preparations, but cluster round it loosely.

The cell as a whole is usually a little smaller than the "neutrophile" and more irregular in shape. In stained specimens the neutrophile is seldom seen with a pseudopod extended, whereas the eosinophile often shows it.

The staining of the nucleus is more even as well as paler than that of the neutrophile, and with the Ehrlich-Biondi stain often has a robin's-egg tint.

The four stages of growth in which we usually find leucocytes in the blood are these:

1. Small lymphocytes, } young cells.
2. Large lymphocytes and transitional forms, } young cells.
3. Polymorphonuclear neutrophiles—adult cells.
4. Eosinophiles—old cells.

5. A fifth variety of leucocyte—the basophilic "mast cell"—has lately been described as a constituent of normal blood, though in very small numbers. In leukæmia it is not very uncommon, but no special significance is attached to it.

With Ehrlich's stain the basophilic granules of this cell are not seen or appear only as clear white spots. Stained with the following solution they are easily seen:

Dahlia (saturated alcoholic solution filtered),	50
Glacial acetic acid,	10–15
Distilled water,	100

Covers should be left twenty-four hours in this mixture, then washed and mounted in the ordinary way. The nucleus is usually polymorphous. Where these basophilic cells belong in the life history of the leucocyte is uncertain, and they have as yet no known clinical significance.

Terms.

No one can feel more unsatisfied with this terminology than the writer. It rests partly on a theory of the origin of the cells ("lymphocytes"), partly on the properties of the nucleus ("polymorphonuclear"), and partly on affinities for aniline dyes ("neutrophile"—"eosinophile").

All that can be said for it is that it discards certain very misleading names like "splenocyte" (a term applied by some to the large lymphocytes according to the now exploded theory that they came from the spleen), or like "small mononuclear" to designate cells not rarely polynuclear.

The cumbrous word "polymorphonuclear" is a shade better than "polynuclear," and that is all to be said in its favor.

It is greatly to be hoped that we may ere long have a new and improved terminology by some competent student. While waiting for this the writer has thought it best to save time and space by speaking of them often as "young," "adult," and "old," with the meaning indicated above.

For some unknown reason we do usually find the leucocytes

only at these four isolated stages of growth (the frequent presence of transitional stages between "small" and "large" lymphocytes has been mentioned as an exception). Apparently they must pass comparatively rapidly through certain stages and remain longer in others, or it may be that they retire out of the peripheral blood at certain periods of the growth.

It is certainly curious how rarely we find a lymphocyte just beginning to accumulate neutrophilic granules. They seem to jump from non-granular to profusely granular, and we rarely see any of the intermediate stages.

Still rarer is it to find any link between neutrophilic and eosinophilic cells. A few instances have been reported (in pathological blood) where both kinds of granules were present in a cell, or granules of an intermediate description. But this has been denied by excellent observers and must certainly be very rare.

Normal Percentage of Each Variety.

In the blood of healthy adults the proportions of the different varieties above described are the following:

Young { small lymphocytes, ...	20–30	per cent.
Young { large "	4– 8	"
Adult (polymorphonuclear neutrophiles), .	62–70	"
Old (eosinophiles), ...	$\frac{1}{2}$– 4	"
"Mast cells,"	$\frac{1}{40}$ $\frac{1}{2}$	"

In infancy the percentage of young cells is much larger (forty to sixty per cent) and the adult cells (polymorphonuclear) are only eighteen to forty per cent.

In a variety of debilitated conditions not usually thought of as definite diseases, the number of young cells is comparatively large and that of the adult cells small. The general vigor and health of the individual can sometimes be estimated simply from the forwardness or backwardness of their blood development as mirrored in the leucocytes. Persons calling themselves well, but never vigorous or active, may show no more than fifty per cent of adult cells, the young cells running up to forty or even fifty per cent.

Not all cases of debility show this change, and we are not yet in a position to say under just what conditions it occurs.

Presumably the conditions are such as decrease the nutritive value of the plasma.

The same change in frankly pathological conditions will be discussed later (page 98).

So far I have spoken only of those changes in the percentages of different leucocytes which are *to* be explained by a more or less rapid metabolism of the cells themselves in the blood, as if they were always sent into the blood as young lymphocytes and lived and died there.

But the eosinophiles often change their number in a way hard to explain on this hypothesis. We know that eosinophiles are present in large numbers in various parts of the body outside the blood-vessels (bone marrow, thymus gland), and in many ways they seem to live their life in comparative independence of the other members of the leucocyte group.

In the free interchange of fluid and cells that is constantly going on between blood-vessels and lymphatic tissues and spaces, it is evident that a part of the life history of the leucocytes goes on outside the vessels, and there is reason to suppose that it is largely or partly outside the vessels that cells of a given age divide and produce others like themselves, while in the blood-vessels they simply grow up without such division. At any rate, we rarely find evidence of mitosis or amitosis in the circulating leucocytes, while in the lymph glands and the marrow, and sometimes elsewhere, such dividing forms are more common.

The bone marrow seems to be such a dividing-place for eosinophiles. They are always numerous there and mitoses are often seen in them. Indeed their number is so small in normal circulating blood that they might almost be said to be there "by mistake," belonging normally elsewhere. Whether or not this has any connection with their very active amœboid properties, I do not know. The "mast cells" are even more "an accident" in the blood, and Ehrlich denies that they are a constituent of normal blood.

An increase of eosinophilic cells in the peripheral blood does not seem to mean simply a change in the rapidity of metabolism, but to point sometimes to a disturbance having relation to the places or functions which produce them. The eosinophile, therefore, more than any other cell normally present in

blood, has value in diagnosis by pointing to the location of a disease (see below, page 100).

Their increase and decrease in the circulating blood does not follow that of the other ripe cells (neutrophiles), in fact is often inversely proportional to it, and they are often markedly increased in a blood otherwise normal, sometimes for reasons wholly unknown to us.

An increase in the lymphocytes or neutrophiles does not occur without other blood changes, and points, not to disease of one place or function, but to general conditions like inflammation or malnutrition.

I have spoken of the eosinophiles and "mast cells" as comparative strangers, though not intruders in the circulating blood. They are thus intermediate between the regular inhabitants (lymphocytes and neutrophiles) and the variety next to be mentioned, which are real intruders—*i.e.*, never found in normal blood. These are the

Myelocytes (Ehrlich).

The normal abiding-place of these cells appears to be the bone marrow, hence their name of myelocytes or marrow cells. They are perhaps the most numerous leucocyte to be found in the marrow, although lymphocytes and polymorphonuclear cells are also to be found there, and eosinophiles are numerous.

I describe them here because they are peculiar to no one disease and are occasional visitors of the blood in conditions on the borderland between the pathological and the physiological (starvation—various intoxications).

The myelocyte (see Plate I.), like the polymorphonuclear neutrophile, is recognizable only by Ehrlich's staining methods. With the Ehrlich-Biondi stain it appears as a spherical cell nearly filled by a large, pale-stained nucleus immersed in neutrophilic granules. You see at once how little it differs from the large lymphocytes (simply in having granules) and from the polymorphonuclear neutrophile (only in the shape of its nucleus). Were it present in normal blood we should undoubtedly consider it an intermediate stage between the large lymphocyte and the polymorphonuclear neutrophile. I see no sufficient reason for thinking otherwise merely because it does not appear in normal

blood. The leucocytes are so cosmopolitan in their habits that we can hardly call them *blood* cells at all. It is better to think of "blood leucocytes," "gland leucocytes," and "marrow leucocytes" (perhaps "skin and mucous membrane leucocytes" too, see below, page 101) and to consider that "missing links" among blood leucocytes are to be looked for among those that live and grow up elsewhere. Presumably the conditions in the marrow (nutrition?) are such as bring out sides of the leucocyte nature suppressed in the blood.

The granules of the myelocyte are precisely those of the adult blood leucocyte and need no second description (see Plate I.). The nucleus, by which alone we distinguish it from the adult blood leucocyte, shows none of the twists and turns characteristic of the latter. Presumably this is due to the fact that the myelocyte is not amœboid and so does not mutilate its nucleus in the trying process of crawling through tissues and vessel walls.

1. The myelocyte nucleus, then, is usually spherical or egg-shaped, and is in close contact with the cell wall for a comparatively large portion of its extent—*i.e.*, if egg-shaped it is placed eccentrically.

2. The absence of amœboid motion and of journeys through tissues leaves the nucleus evenly and moderately stainable throughout, while the amœboid blood leucocyte, through the wear and tear of its migrations, gets its chromatin irregularly distributed, condensed here, pulled out thin there, and hence stains unevenly or is mottled.

Not infrequently the nucleus shows signs of old age (vacuoles) or of mitosis, and occasionally we find two nuclei at the poles of the cell. It is then to be distinguished from the adult blood leucocyte (polymorphonuclear neutrophile) by the fact of its having the nucleus in close contact with the surface of the whole cell for a comparatively large portion of its extent, while in the adult blood leucocyte the nucleus abruptly leaves the surfaces again if it chances to approach it. The polynuclear myelocyte is also to be distinguished from the polymorphonuclear neutrophile by the *even* staining of the nucleus in the former.

Size of Myelocytes.

Every account of the myelocyte which has come to my notice speaks of them as very large cells, the largest variety of leucocytes ever seen in the blood.

This is true of many of them; diameters of 18–21 μ are not uncommon, but we also find them of *every* other size down to 10–11 μ diameter, that is, down to the size of a lymphocyte. This is true both of the myelocytes in the circulating (leukæmic) blood and of those in the marrow. No distinction from other varieties of leucocyte can be based on size alone, unless we say their *average* size is greater than the average size of the leucocyte. Perhaps the following table may be of interest:

Average diameter of 100 myelocytes = 15.75 μ.
" " " 100 polymorphonuclear neutrophiles = 13.50 μ.
" " " 100 "large" lymphocytes = 13 μ.
" " " 100 eosinophiles = 12 μ.
" " " 100 "small" lymphocytes = 10 μ.
" " " 100 red corpuscles (normal) = 7.5 μ.

Eosinophilic Myelocytes.

Under the same conditions where we expect to find the ordinary (neutrophilic) myelocyte, we often find a small number of cells identical with them in all respects, except in possessing eosinophilic in place of neutrophilic granules. Such cells are found in abundance in the marrow, and this fact together with the resemblance to the ordinary myelocyte both in morphology and in the conditions of their occurrence, seems to me to justify the term *eosinophilic* myelocyte.

Cornil's "Mark Cells."

By most observers these are supposed to be the same as Ehrlich's "mark cells" or myelocytes. Cornil worked before the days of Ehrlich's staining methods and therefore before the presence of neutrophilic granules could be used to distinguish a myelocyte from a large lymphocyte. Cornil's description of them would answer for either. Schreiber considers Cornil to have discovered a different variety of non-granular cell, but the

description of it given by Schreiber seems to me to leave it indistinguishable from a large lymphocyte.

Mononuclear Neutrophiles.—Capps[1] observed in general paralysis of the insane a variety of leucocyte possessing a deep-staining centrally placed nucleus like that of a lymphocyte, but containing also neutrophilic granules. He considers it either a variation from the ordinary type of marrow-bred cell visiting the blood temporarily, or more likely an ordinary lymphocyte in which the granules have developed before the nucleus has become polymorphous. Thayer has observed similar cells, but has given no explanation of them. Klein[2] mentions them under the name above given and figures them in his plate, but does not comment on them.

So far I have described the *type cell* of each variety. As we should expect, atypical forms are numerous. Some of the commoner ones are as follows:

1. Young cells whose nucleus is pale blue instead of dark blue.
2. Cells more developed but still non-granular, whose protoplasm has evidently forsaken them.
3. Cells on the borderland between the "marrow cell" and the "adult blood leucocyte," the nucleus having some of the characters of each variety.
4. Cells the nature of whose granules we cannot settle (eosinophilic or neutrophilic).

Other rare varieties will be mentioned under leukæmia.

[1] American Journal of Medical Sciences, June, 1896.
[2] Volkmann's Sammlung klin. Vorträge, December, 1898.

PART III.

GENERAL PATHOLOGY OF THE BLOOD.

CHAPTER VI.

UNEQUAL DISTRIBUTION OF BLOOD—PLETHORA—DILUTION AND CONCENTRATION OF THE BLOOD.

I. *Unequal Distribution.*

How far is the single drop used for blood examination typical of the whole?

It has been experimentally proved that specimens of the blood of the smaller venous and arterial twigs do not differ from each other materially in corpuscular richness. Capillary blood is slightly richer in corpuscles than that either of veins or of arteries. But as capillary blood is everywhere of the same corpuscular richness, we may consider one capillary network or set of venules as typical as another, provided our technique is good, that is, provided lymph is not squeezed into the drop by strong pressure. It is indifferent, therefore, so far as accuracy is concerned, whether the drop of blood be obtained from one or another part of the body. All standard estimates of the number of corpuscles per cubic millimetre of normal blood refer to capillary blood.

2. *Apparent Polycythæmia.*

So far we are speaking of normal conditions. It is a familiar fact, however, that the vessels of a given part of the body can be overcrowded with blood, *e.g.*, by the use of an Esmarch bandage. A drop taken from such a part would certainly not be typical. Now as the same effect can be produced by a variety of diseases, under these conditions we must modify considerably any inferences made from examination of a single drop.

Such conditions, entailing a false polycythæmia or apparent increase in the number of corpuscles are:

I. Any disease involving either (*a*) general cyanosis or (*b*) cyanosis of the part from which the drop of blood is drawn.

(*a*) *General cyanosis* results either from cardiac insufficiency (valvular or parietal disease of the heart itself, blocking of the lung circulation by emphysema or thrombosis), from insufficient aëration of the blood (pneumonia, congenital malformation of the heart), interference with the heart's action by pressure of tumors, effusions (pericardial, pleural, peritoneal), or enlarged organs (liver, spleen), or from vasomotor disturbances. It is evident that some of these conditions (*e.g.*, congenital heart disease) may not involve any peripheral *stasis* at all, and in the absence of this it is not easy to account for the increased number of corpuscles in the drop. Some observers have supposed that there is a real overproduction of blood cells under these conditions; others suppose that the life of the individual corpuscle being lengthened, reproduction of cells at the normal rate soon leads to the "glut." There seems to be no reason to suppose that there is in these cases any unequal distribution of cells in favor of the periphery, such as is obviously the condition in ordinary cyanosis with stasis. Whatever the explanation may be, there is no doubt of the fact that general cyanosis from any cause whatever produces an increase of cells in a drop such as we usually examine.

The cases of cyanosis which I have classed under "vasomotor" (for want of a better explanation), cases in which, in the absence of disease in any organ, the skin and mucous membranes are persistently and markedly bluish, are not very uncommon. I have seen three such, all in stout, elderly women. In one the cells in a drop of blood from the ear, finger, or toe were more than *double* the normal number (see below, page 67).

(*b*) *Local Cyanosis.*—The pressure of a tumor, or any other hindrance to the circulation of any part, may give a similar increase in the number of corpuscles in a measured amount of blood from that part. Here again vasomotor conditions may cause cyanosis and apparent polycythæmia.

In markedly cyanotic patients the count of red cells is notably above normal, we should naturally guess the reason, and make

allowances. Error is more likely to arise where we have cyanosis in a person whose blood is poor in red corpuscles. The combination of these two factors may give us a normal blood count and lead us to overlook the anæmia. Thus a person might have really a severe anæmia and yet the count of red cells be actually above the normal. This element of stasis should never be lost sight of. Many high counts reported in pneumonia or hysteria are to be explained by abnormalities not of *production* or *destruction* but of *distribution* of the blood cells.

II. Certain patients, whose circulations are feeble without being feeble enough to produce actual cyanosis, first give us evidence of the fact by an increase in the count of blood corpuscles in a given amount of peripheral blood. Following up the hint thus given, one may sometimes be brought to note and investigate an element in the case which might otherwise have been lost sight of.

With these exceptions the drop of blood taken at the periphery is typical. We have next to consider some *general* conditions under which a person's whole blood may be inferred to be abnormal from the findings in a drop taken from the periphery. Consideration of *special* diseases will follow later.

Full-Bloodedness (Plethora) and its Opposite.

There is no direct evidence for the existence of any long-standing over-filling or under-filling of the blood-vessels; there is a good deal of experimental evidence to show that if by artificial means we succeed in forcing into the vessels an abnormal amount of fluid (transfusion of blood or normal salt solution—large draughts of water), it does not stay there many hours, but comes out by the kidneys.

The red-faced persons popularly known as "full-blooded" show no abnormalities in their blood discoverable by any means of investigation known to us. The condition is probably dependent on the presence of a rich capillary network near the surface of the skin, or a dilatation of individual venules and arterioles at the periphery. Such a person may be markedly anæmic without any considerable changes in the color of the face. The fact that people of such complexion often end their lives with a ruptured cerebral artery is due presumably to the

circumstance that "high living" produces in the same individual dilated peripheral capillaries and weakened arterial walls.

Temporary increase or diminution in the amount of fluid within the vessels can be brought about not only by a change in the mechanical conditions of pressure and osmosis, but by any influence affecting the tone of the peripheral vessels. We have then:

(*a*) *Temporary serous plethora or dilution of the blood* from transfusion of fluid in large amounts or its ingestion by mouth or rectum.

(*b*) From decreased blood pressure, as in acute failures of compensation in cardiac disease.

(*c*) From vasomotor dilatation.

As an example of this last Grawitz reduced the specific gravity of the blood from 1041 to 1038.7 within eight minutes by the inhalation of nitrite of amyl. This decrease of specific gravity can only mean an increased amount of watery constituents in the blood, as there was no evidence of any destruction of the heavier elements of the blood, and only water (and chlorides) pass through the vessel walls easily. In the above case the specific gravity was again at 1041 within a few minutes.

(*d*) In cases of severe anæmia which recover, the blood regeneration may attain such vigor that the number of red cells shoots up *above* normal, even as high as 7,700,000. This is *temporary cellular plethora* or polycythæmia.

(*e*) The same condition can be temporarily produced by transfusion of actual blood from one individual to another. It lasts but a few days as a rule.

The polycythæmia of the new-born will be discussed later.

Concentration of the Blood.

It is obvious that influences opposite to those producing temporary full-bloodedness will produce temporary lack of fluid within the vessels. So acute diarrhœa, purgation, deprivation of liquids (as in starvation), rapidly accumulated serous effusions, profuse vomiting or sweating (by skin and lungs) produce a temporary *concentration of the blood* by draining out its diffusible elements (water chiefly). All these influences are transitory. More permanent drains on the system, like chronic diarrhœa, diabetes insipidus or mellitus, or long-standing suppurations, tions of blood volume that we can measure the amount lost by

show no evidence of lessening the volume of blood in the vessels. They drain albumin out of the serum and corpuscles and so decrease the weight of the blood (see below, page 71), but the blood volume is not changed. Indeed, any influence has to work very quickly in order to concentrate the blood, for in an astonishingly short time the other tissues repay the vessels their loss of fluid and the normal blood volume is restored.

The same temporary effects can be produced by influences constricting the vessels (cold, pain, suprarenal extract), and a concentration of the blood results which lasts a few minutes or hours.[1]

In all these interchanges of contents between the blood-vessels and the other tissues it is, as above said, the watery elements chiefly that change. The red cells are not affected by the give-and-take of the vessels and tissues, and although cold produces in the peripheral circulation an increase in the number of white cells greater than can be accounted for by simple concentration, the weight of evidence seems to be against any new production of cells and in favor of a change only in distribution, the white cells accumulating at the periphery.

Now as the number of cells is not affected by these temporary variations in the volume of liquid within the vessels, it follows that the number to be counted in a cubic millimetre, though typical of the whole blood *at that time*, is not to be reckoned from in the ordinary way. For example, after a severe diarrhœa or in phthisis after a night-sweat the blood may be temporarily so concentrated that we find 6,000,000 or more red corpuscles per cubic millimetre. Under normal conditions of the blood mass we should infer from such a count that the body contained one-sixth more red corpuscles than usual. Here obviously it only means (if anæmia is absent) that the blood mass is reduced by one-sixth by concentration. It is only in such sudden reduc-

[1] Oliver has shown recently (Lancet, June 27th, 1896) that any influence causing rise of blood pressure will slightly concentrate the blood. Thus raising the arm over the head and holding it there by muscular effort slightly concentrates the blood in that arm. Electrical stimulation or massage of the arm has the same effect. *Lowering* blood pressure, as when the arm is supported *passively* over the head, dilutes the blood. This confirms the results of Mitchell (Med. News, May, 1893) and of Chéron (Comptes Rend. de l'Acad. d. Sciences, 1896, No. vi.). Oliver uses a new method for estimating the number of red cells, the accuracy of which has not yet been tested by others.

5

this method. Long-standing causes of drain on the plasma might at any time act as destroyers of red corpuscles as well, through the changes in the nutritive fluids in which they live.

Further, it is only where we know the number of corpuscles just before the sudden drain on the plasma comes, that we can measure the amount of plasma lost by the amount of *apparent* increase in the red cells. Stasis and any other cause that heaps up corpuscles at the periphery must also be excluded before we can judge of the loss of plasma in this way.

The conditions of an abnormal concentration of the blood are those already alluded to as temporarily sucking away its watery constituents, namely:

(*a*) Watery diarrhœa, especially in cholera and other acute diseases accompanied by diarrhœa;

(*b*) Large and rapidly accumulating serous effusions (slow accumulations would give time for the blood to take up water from the tissues and make up for its loss);

(*c*) Profuse sweats;

(*d*) Persistent vomiting or starvation of liquids;

(*e*) Increased blood pressure (exercise, massage, electricity).

Blood already lacking in red cells, if suddenly concentrated by such a loss of fluid, might deceive us into supposing it normal, because the number of cells in a cubic millimetre might be normal. *In the presence, therefore, of any such reason for concentration of the blood, we should always modify our ordinary methods of inference from the blood count.* For example, v. Limbeck records a case of hepatic cirrhosis with ascites, where before tapping the ascites the count of red cells was 3,280,000 per cubic millimetre. Within twenty-four hours after tapping there were 5,160,000 cells per cubic millimetre, the reaccumulation of the ascitic fluid going on so fast that the blood was unable to adjust itself and became overconcentrated. A careless observation might have inferred a great gain in the corpuscular richness of the whole blood, when in fact not a corpuscle has been gained and those present have probably grown poorer in albumin.

Dilution of the Blood.

Causes of temporary *dilution of the blood* are less common than those of temporary concentration.

Immediately after the inhalation of nitrite of amyl or the ingestion of a large amount of fluid by mouth or rectum, the blood would be diluted so that a blood count would show a diminution in the number of cells per cubic millimetre, which yet would be due to no changes in the number of red cells in the body, and might be wrongly taken for an anæmia. The dilution in cases of heart disease will be discussed later (see p. 256). Any condition involving *lowered blood pressure* has the effect of diluting the blood by allowing the entrance of perivascular lymph.

Summing up the discussion so far: There is no evidence for a *chronic* plethora nor for a chronic diminution in the volume of the blood. Where such takes place temporarily, it is by the addition or subtraction of water and salts only, and not of the corpuscles or organic materials, so that we must guard against false inferences from the resulting apparent increase or decrease of corpuscles per cubic millimetre.

But although there is no positive evidence of a true increase in the whole amount of blood in the vessels (except temporarily), there are some conditions which lead to an increased richness of the *peripheral* blood in red corpuscles even after excluding the influence of stasis or loss of fluid. Such a condition of what *appears to be* true polycythæmia is found:

1. In persons living at high altitudes;
2. In persons suffering from phosphorus or CO poisoning.

1. The Blood in High Altitudes.

The polycythæmia of those living at high altitudes increases the higher one goes. Köppe[1] gives the following tables:

Place.	Height above sea level.	Red cells.	Author.
Christiania	O	4,974,000	Laache.
Göttingen	148 metres	5,225,000	Schafer.
Tübingen	314 "	5,322,000	Reinert.
Zürich	414 "	5,752,000	Stierlin.
Auerbach	425 "	5,748,000	Köppe.
Reiboldsgrün	700 "	5,900,000	"
Arosa	1,800 "	7,000,000	Egger.
The Cordilleras	4,392 "	8,000,000	Viault.

[1] Münch. med. Woch., 1890, No. 41.

This extraordinary change takes place within two weeks of the time of taking up residence in a high place, and independent of any change in diet or manner of living. The sick and the well are equally affected and animals show similar changes. The hæmoglobin is also considerably increased, although it lags somewhat behind the corpuscles.

Köppe states that the individual corpuscles under these conditions are so much smaller that their volume in a given amount of blood (as determined by the hæmatocrit) is not increased at all.

On returning to low land, the blood returns within a short time to its normal condition.

Many explanations have been offered for this interesting phenomenon. If it were a true new production of corpuscles we should expect some signs of blood destruction (icterus, hæmoglobinuria) on returning to the sea level. But there are no such signs. On the other hand, if the polycythæmia were a simple result of concentration due to the dryness of the high air, one would expect that the blood would quickly adapt itself, as in other (temporary) concentrations, by taking up water from the tissues. But in fact it does not do so. Possibly it may be explained, as Fick suggests, by a lengthening of the life of individual cells.

2. Phosphorus and CO Poisoning.

The polycythæmia of acute phosphorus poisoning may reach as high as 8,650,000. This may be partly explained by concentration due to the occurrence of vomiting, but in some cases the increase seems out of proportion to the amount of vomiting.

With illuminating-gas poisoning there is usually no vomiting to speak of, and the cause of the marked increase in the red cells is unknown. Von Limbeck in two cases showed respectively 6,630,000 and 5,700,000 red cells. Munzer and Palma[1] record 5,700,000. The white cells are also increased (see below, page 94).

Possibility of a true Plethora.

Although there is no *direct* evidence that the whole blood mass in its relation to the weight of the body ever varies more

[1] Zeit. f. Heilk., vol. 15, p. 1.

than temporarily from the traditional 1 to 13, one can hardly help getting the *impression* from certain patients that their blood mass *is* diminished, though we cannot prove it. Thus in certain cases of phthisis in which in spite of all the signs and symptoms of anæmia the blood count is normal, and simple concentration of a really anæmic blood seems to be excluded by the absence of a cause for such concentration, we cannot help thinking that the whole amount of blood is too small. Again, it is possible that in individuals who eat and drink much and exercise little the blood-vessels may gradually accommodate themselves so as to hold a *large* bulk of liquid, and thus a true plethora or "full-blooded" condition might be brought about. Experiments show, however, that fat, "sedentary" animals (pigs) have *less* blood in proportion to their weight than lean, active animals (horses, dogs). Pigs' blood is only one twenty-second of their total weight, while horses' is one-tenth.

Young, fast-growing animals have relatively more blood than adults, and males more than females. Our impression that old people are more or less "dried up" gets some support from the analogy of these animal experiments.

Until some method is devised for estimating the total amount of blood during life, we shall never be sure upon this point.

CHAPTER VII.

ANÆMIA AND HYDRÆMIA.

1. ANÆMIA.

IN the absence of any proof that the total volume of blood can be more than temporarily diminished, our definition of anæmia must be this: *A deficiency in corpuscle substance, i.e.*, a deficiency in red corpuscles, in hæmoglobin, or in both.

It is important to bear in mind that the color of the skin is not a safe guide in judging whether a person is anæmic. Thus out of 100 cases shown to be anæmic by actual blood examination, Townsend[1] found a good color in the cheeks of 4 and a fair color in 7 others. Eighty-nine were pale. The color of the lips is but little better as a guide, as the following table from Townsend's article shows:

Table of Color in One Hundred Cases of Anæmia.

	Pale.	Fair.	Good.
Nails	95	5	0
Cheeks	89	7	4
Tongue	84	15	1.2
Lips	76	21	2.4
Conjunctivæ	64	25.5	10.5

My own impression would be that the lips and conjunctivæ were better guides than they are shown to be in this table.

In examining the color of the nails, the fingers should be flexed, as full extension may partly cut off the circulation under the nails.

A. K. Stone[2] and his assistants estimated the hæmoglobin of 189 female patients who looked anæmic, and found over 75 per cent of hæmoglobin in 89, or nearly one-half of them. For

[1] Townsend: Boston Medical and Surgical Journal, May 28th, 1896.

[2] Boston Medical and Surgical Journal, August 23d, 1894.

a woman a hæmoglobin percentage of 75 per cent or more means practically normal blood.[1]

The most striking example of the fallacy of judging of anæmia by the color of the skin and mucous membranes is in the so-called "*tropical anæmia.*" Practically all persons belonging to white races who take up their residence in the tropics acquire after a time an extreme pallor of the skin and mucous membranes, and this appearance has usually received the title of "tropical anæmia." It turns out, however, from the careful studies of several different investigators, that the blood of such persons shows absolutely no anæmia or other variation from the normal. The appearance of the skin is probably due to the action of the extreme climate on the peripheral nerves and vessels. Tropical anæmia is a condition not of the blood, but of the skin and subcutaneous tissues.

Every one's experience includes a few persons who are perfectly well despite an almost bloodless condition of the skin.

On the other hand, anæmia may exist where there is a good color in the face (see above, page 63).

We are to judge of anæmia, then, solely by the blood examination, and this judgment can be accurately made on the basis of the small fraction of a drop used for examination, *provided* always that our technique is good, and provided we make allowances for a considerable error wherever there is reason to suppose that any venous and capillary stasis is present, or that the blood is temporarily concentrated or diluted (see above, page 59).

Distinction between Primary and Secondary Anæmia.

In one sense all anæmia is secondary. It is due to some cause, a symptom in a chain of events. But in some cases we know the cause and in some we do not.

(*a*) *Primary anæmia is that in which the causal factors are either entirely unknown or are insufficient to cause so severe a disease.* This division, like most of our statements about the blood, is a rough-and-ready one, held to provisionally until a better classification is discovered. It has a certain utility if not used with any less simple meaning than that given above.

[1] Where the hæmoglobin is high the number of corpuscles is never considerably diminished.

In view of our ignorance of the blood-making functions, there is little difference between saying that a primary anæmia is a disease of the blood-making organs and saying that it is one whose cause is unknown, especially as the pathological appearances in the bone marrow recorded in cases of so-called primary anæmia do not differ from those which can be brought about experimentally by bleeding. There is no evidence that there are any primary diseases of the blood-making functions. A case of secondary anæmia is one in which we have an obvious cause such as hemorrhage or malaria for the loss of corpuscle substance. Remove the cause and the anæmia ceases. Sometimes, however, after removal of the cause, *e.g.*, after cure of a case of syphilis, the anæmia set agoing by the syphilis persists. Here we have to say that the anæmia has changed from "secondary" to "primary," possibly through some alterations produced in the blood-making functions which disable them from making up the lost blood, even though the drain upon it is no longer going on. On the other hand, there are few cases of "primary" anæmia who cannot recall some event in their past lives sufficient to account for *a certain grade of anæmia* (*e.g.*, a nervous shock, a hemorrhage, an attack of tertian malaria). Yet if the anæmia that occurs after so slight a cause is of the pernicious or fatal type, we may fairly call it "*primary*." By this we mean that though the "cause" assigned might produce *some* anæmia, it was not sufficient to produce *this* fatal anæmia and has presumably little or no connection with it. "Primary" means not the absence of *any* cause of anæmia in the history, but the absence of any *sufficient* cause so far as is known.

An attack of tertian malaria or a history of bleeding piles does not cause fatal anæmia in 999 out of 1,000 people who have such a history. In the 1000th it is a case of *post hoc* and not *propter hoc*. Given the unknown cause that *does* lead to "primary" anæmia, and it might be that a pregnancy or the presence of intestinal parasites would act as the straw that breaks the camel's back; but *the important causal factor is the unknown factor.* It is, then, by their etiology and not by their symptoms or by the blood examination alone that we distinguish primary from secondary anæmia.

It is true that in the majority of cases we can tell from the blood examination alone whether a case is without known cause

(= "primary") or symptomatic (= "secondary"). But there appear to be enough exceptions to this rule to make us cautious about stating it as a law.

ANÆMIA =	Primary =	Chlorosis, Pernicious anæmia,	To be discussed under Special Pathology of the Blood, Chapter VII.
	Secondary.		

Secondary Anæmia.

I. *First Stage.*—I defined anæmia above as *a diminution in corpuscle substance.* In the milder types of this condition the number of red corpuscles is not diminished at all, but the individual cell is small, pale, and of light weight, through loss of nitrogenous matter. This is appreciated:

(*a*) As a lack of coloring matter;

(*b*) As a lowering of the specific gravity.

In the mildest grades of secondary anæmia there are no further changes. Such cases are those due to errors in hygiene—bad air, poor food, lack of light or exercise—to small hemorrhages, and to the earlier stages of the diseases next to be mentioned.

The lack of coloring matter is usually not present in every cell, as is seen in the stained specimens. Some are very pale at the centre, while others are well stained.

II. *Second Stage.*—Usually the next changes to appear are, like those already mentioned, *qualitative,* the number of red cells still remaining normal or approximately so.

The individual cell as seen in fresh preparations is more or less deformed and varies from its normal diameter, dwarfed forms usually being commoner than the giant forms. These variations in size and shape are sometimes termed "*poikilocytosis,*" and the dwarf and giant forms are called respectively microcytes and macrocytes.

Maragliano[1] has included the above changes, together with others about to be described, under the heading of

Necrobiosis in the red corpuscles, attributing them to a pathological condition of the serum.

The changes united under this heading may be divided for convenience' sake into:

(*a*) Endoglobular changes.

[1] XI. Cong. f. Inn. Med., Leipzig, 1892.

(*b*) Poikylocytosis and crenation.

(*c*) Changes in staining properties.

(*d*) Changes involving motility in the corpuscle as a whole, or in parts of it.

(*e*) Decrease in the average diameter of corpuscles with loss of the power to form rouleaux.

All these changes may be watched in normal blood outside the vessels, as necrosis gradually comes on from contact with the air. Under pathological conditions the same changes may occur *outside the body*, but more quickly than usual (as other diseased tissues decompose more quickly after death than those of a sound man suddenly killed), or *inside the body*.

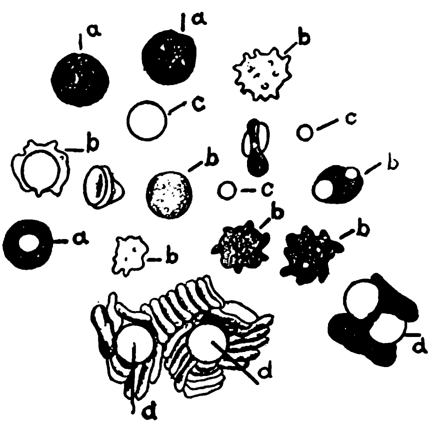


FIG. 18.—Degenerative Changes in Red Cells.

(*a*) *Endoglobular Changes* (see Fig. 18, *a*).—These consist in the appearance of clear hyaline spaces of various shapes within the corpuscle, round, triangular, rod-shaped, etc. In the fresh specimen they change their shape rapidly and continually; in dried and stained specimens they appear as sharply outlined light spaces in the corpuscle. In normal blood these changes occur after thirty to seventy minutes outside the vessels. In some pathological conditions specimens show them the instant the blood is collected, and presumably they were present before it left the vessels.

(*b*) *Crenation and Poikilocytosis* (Fig. 18, *b*).—What we ordinarily know as crenation in the corpuscles is the same sort of process which, occuring within the vessels, we call poikilocytosis. A lump rises at one or more points in the corpuscle, becomes more pointed, and gradually the whole cell acquires amœbȯid motions, assuming in succession the various shapes with which we are familiar in poikylocytes.

(*c*) The pointed projections may break off and move about actively in the plasma. These motions, as well as the preceding

amœboid movement of the whole corpuscle, are to be explained as irregular contractions of the necrobiotic protoplasm, similar in a general way to the actions of a hen after its head is cut off. These motions are not to be confounded with the finer Brownian or "molecular" movement to be seen in any healthy cell. The small bits broken off (Fig. 18, *c*) are doubtless the dwarf cells seen in dried and stained preparations. Curiously enough, these fragments tend again to assume the biconcavity characteristic of normal cells, as a drop of fat breaks into smaller but similar drops.

(*d*) *Changes in Staining Properties.*—Normal red corpuscles have affinity only for acid stains (eosin). The same degenerative changes that lead to the alterations in shape and size above described alter the staining properties of the cell as well, so that it takes up two or three colors (according to the number present in the stain), either as a diffuse mixture or irregularly, some parts of the cell taking color differently from others. This has been termed a "*polychromatophilic*" or degenerative change. Some observers have supposed it to be rather of the nature of *regeneration*, believing that the cells take color in this unorthodox way because they are half-developed, but the weight of evidence is that they are degenerative changes.

(*e*) In many secondary anæmias, especially in those associated with inflammations, the average diameter of the cells is lessened, and the rouleaux are not formed.[1]

(*f*) Cells may lose their hæmoglobin altogether, leaving only the shell of the corpuscle behind (see Fig. 18, *d*).

Now all these necrobiotic changes are characteristic of the severer grades of secondary anæmia such as occur in cancerous cachexia, phthisis, nephritis, etc.

The changes of staining affinity are less common than the others, and usually represent the severest grades of anæmia, but they have also been noted occasionally in smallpox, measles, scarlet fever, typhus, and purpura.

In pernicious anæmia they are, as a rule, much more common than in any other disease. Maragliano considers these degenerative changes to be due to toxic plasma. A lessened resistance to the ordinary plasma-environment on the part of the red cells

[1] But in the severest forms of anæmia the diameters are apt to be increased (see below, Pernicious Anæmia).

would also explain them, and in such affections as paroxysmal hæmoglobinuria it seems the most probable cause. In syphilis the abnormal sensitiveness of the red cells to the influence of mercury seems another instance where the red cells are immature, decrepit, or weak. In syphilitic children, for instance, mercury easily gives anæmia, while in healthy children it does not. This will be discussed more fully under syphilis.

The necrobiotic phenomena above described have been observed by Maragliano in carcinoma, lead poisoning, leukæmia, pernicious anæmia, purpura, cirrhotic liver, nephritis, pneumonia, malaria, typhoid, erysipelas, and tuberculosis. Celli and Guarnieri (*Fortschritte der Medicin*, 1889, No. 14) found them in measles and scarlet fever. Weintraub (*Virchow's Archic*, Vol. 131) noted them in epilepsy, pyæmia, and catarrhal jaundice.

A decreased resistance to pressure of electric currents and other influences has also been noted by v. Limbeck in some cases.

Such weakening of the red cells experimentally produced in animals by poisons has been found (Mya and Sanarelli, *Arch. ital. di Biolog.*, XVII., 1892) to increase the susceptibility to infectious diseases.

III. *Third Stage.*—Here the number as well as the quality of the red cells begins to suffer. So far I have mentioned only the qualitative changes in secondary anæmia and have purposely made these changes more prominent than the actual diminution in the count of red cells, because it is only comparatively rarely and in very marked cases that the diminution in red corpuscles is considerable. The blood characteristic of most cases of secondary anæmia is one in which the number of red cells is approximately normal.

The important exceptions to this rule are: 1. The anæmias of infancy and early childhood. 2. Large hemorrhages (soon after their occurrence). 3. Malaria. 4. Acute septicæmia.

The direct and rapid destruction of the corpuscles by the malarial organism or hemorrhage account for this. Of sepsis and the anæmias of infancy we shall speak later.

IV. *Fourth Stage.*—The blood of secondary anæmia shows often evidence not only of degeneration and destruction of the cells but also of regenerative changes, namely:

Nucleated Red Cells.

These are usually divided into three groups

(*a*) Normoblasts.
(*b*) Megaloblasts.
(*c*) Microblasts.

Normoblasts.

(*a*) The first are normally present in moderate number in the bone marrow of healthy persons, and in great numbers in the marrow after hemorrhage. They are generally considered to be a younger stage in the life of the corpuscle than the non-nucleated forms seen in the circulating blood. Hence the appearance in the peripheral circulation of this form of nucleated cell is considered to mean that, in the comparatively plentiful reproduction of red cells called forth in the marrow by an anæmia, a certain number of red cells leave the nursery (the marrow) before they are grown up and circulate for a time in their immature state. A normoblast, then, represents an immature red corpuscle (see Plate IV.).

In size and color it is like an ordinary red cell except that we find, usually somewhat to one side of it, a round nucleus about one-half the diameter of the whole cell. With the Ehrlich-Biondi tricolor mixture, this nucleus stains very deep blue, nearly black, and is sharply outlined against the pale yellow of the cell body round it.

As the cell grows older it often pushes its nucleus out, and accordingly in many instances we actually see the nucleus projecting over the edge of the corpuscle, or half out of it, and occasionally we find it lying beside the corpuscle from which it has just emerged.[1] Not infrequently, of course, the cell lies so placed that this expulsion of the nucleus happens to be "upward," or toward the eye of the observer; in this case we notice that the nucleus is more or less out of focus when the cell body is *in* focus, and that when we draw up the lens a little it becomes clearer.

Very frequently the nucleus has toward the centre a light spot, sometimes so brilliant that it looks like the reflection of

[1] According to Ehrlich a new non-nucleated red cell is formed from this extruded nucleus.

light from the surface of a drop of ink or any dark liquid, what artists call the "high light." Occasionally there are several of these light spots in a nucleus, or it may be all light blue-gray except a dark blue rim. This is the commonest type of normoblast. But now and then we meet with one when the nucleus is more or less separated into two or more pieces. These pieces are usually connected by pale-staining "bridges," perhaps radiating from a centre so that the nucleus is "rosette-shaped," or it may take any one of a large number of different shapes. The parts of the nucleus which are nearest the periphery of the cell usually stain deeper than the "bridges" which join them.

Sometimes the nucleus breaks apart completely and we find two or more separate unconnected nuclei within the single cell.[1] Or one of the pieces may be outside the cell and the others inside.

Rarest of all is the appearance of true mitosis in the nucleus of a normoblast.

Megaloblasts.

(*b*) The typical megaloblast as usually described is so unlike the normoblast that we should not naturally think of them as near relations.

It does not occur anywhere in the healthy adult body, not even in the bone marrow. In the fœtal marrow and in the marrow and circulating blood of very grave forms of anæmia it is to be found, usually in company with a certain number of normoblasts.

Ehrlich has described it as the sign or product of a wholly different type of blood formation, namely, the *fœtal type*, and considers those anæmias in which it occurs as tending to a return of the blood to the fœtal state. Here the nucleus, instead of being extruded, is absorbed, and does not give rise to a new cell, so that there is no tendency to regeneration of the blood such as is expressed by the normoblast. Hence he regarded the presence of megaloblasts as a bad prognostic sign, and believes that a pernicious or fatal anæmia was characterized by an excess of these cells over the normoblasts. He recognized that they might be found in various milder forms of anæmia; but here the *prevailing type* is the normoblast, and regeneration may be more active than degeneration.

The *typical megaloblast* is an abnormally large cell (11 to 20 μ

[1] Apparently the nucleus is sometimes absorbed and not pushed out.

PLATE IV.

(*a*) In the "typical megaloblasts" (*m, m, m, m*) note the white line around the nucleus, the variations in its tint, and, in two of them, the discolorations of the protoplasm (polychromatophilia), especially near the nucleus. The lower of the two cells in karyokinesis shows this best.

(*b*) Note in the cells with dividing nuclei (*D, D, D, D*) the grayish "bridges" joining the separate parts of the nuclei.

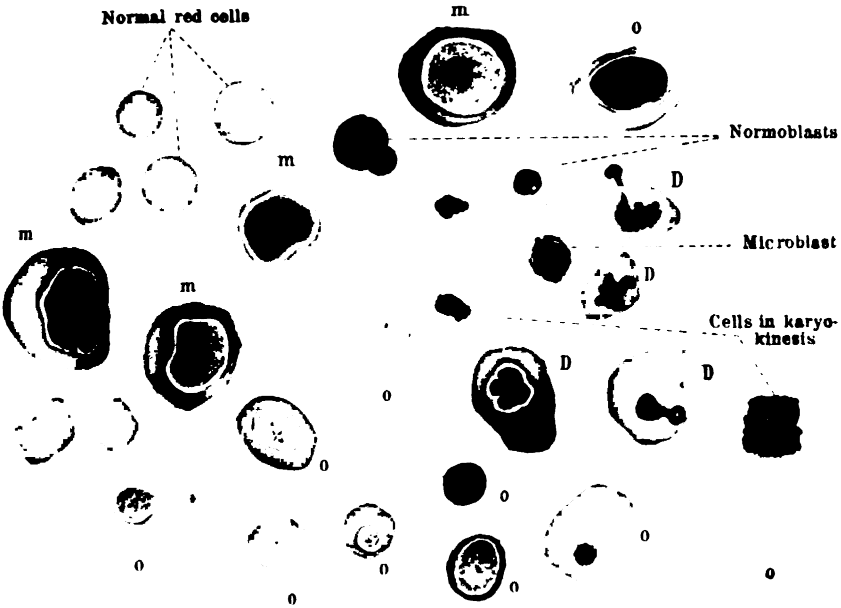
(*c*) In the *microblast* note the ragged edge of the protoplasm.

(*d*) In the lower portion of the plate ("*cells deformed in size or shape*") an actual field from a case of pernicious anæmia was copied. *Macrocytes* (or large cells), *microcytes* (or small cells), and misshapen cells or *poikilocytes* are shown.

(*e*) The "*polychromatophilic cells*" in the lower right-hand corner were stained with the same mixture as those to the left of them, but have taken up other colors besides the orange G, which alone is taken up by normal red cells.

Examination of the Blood.

PLATE IV.



Varieties of Nucleated Red Cells.

m. m. m. m.-Typical megaloblasts D. D. D. D-Cells with dividing nuclei

o. o. o. o. o. o. o.-Other (unnamed) varieties of nucleated red corpuscles.

Scale of μ

Cells deformed in size or shape

R. C. Cabot fec.

Lith. Anst v. E. A Funke, Leipzig.

in diameter, frequently showing marks of degeneration (polychromatophilia) in its protoplasm, which is therefore brownish or purplish with the Ehrlich-Biondi stain. Its nucleus is very large, filling most of the cell, and contrasts with the normoblast nucleus not only by its greater size but by the pale, even stain which it takes up. The commonest color of the nucleus with the Ehrlich-Biondi stain is pale green or robin's-egg color. Sometimes it is not stained evenly but dotted over with purplish granules arranged in a mesh like the knots in a fish-net (see Plate IV.).

Outside the nucleus there is usually a narrow band of clear white, apparently an empty space, separating the nucleus from the encircling protoplasm. The protoplasm close round this colorless ring is usually stained more deeply than the rest of the cell. Cracks and "flaws" are sometimes to be seen in the protoplasm, giving evidence, as its purplish stain does, of the necrobiotic changes described by Maragliano.

The outline of the whole may be quite circular: oftener it is oval or somewhat irregular, but rarely much deformed.

Microblasts.

(*c*) Microblasts, which are rarer than either of the varieties just described, consist of a nucleus like that of a normoblast or smaller, and contained in a cell body *smaller* than the normal red corpuscle. In the writer's experience the cell body is usually reduced to a few shreds of discolored protoplasm hanging about the nucleus (see Plate IV.). Their significance is usually supposed to be that of megaloblasts.

"*Atypical Forms.*"

Unfortunately for our terminology and for Ehrlich's theory of two separate types of blood formation, we find in some cases a variety of other appearances in the nucleated red cells. Sometimes we find in a given specimen of blood only typical normoblasts, microblasts, and megaloblasts, and accordingly can easily reckon up the number of each kind and see which type of blood formation predominates. More often there are a few cells present, about the classification of which we cannot come to a decision, and I have occasionally seen a specimen of blood containing a large number of nucleated red cells *no one of which* could

strictly be classed *either* as a normoblast, a megaloblast, or a microblast, as these are usually defined.

This I have attempted to illustrate in Plate IV. Judging from appearances we should naturally suppose these to be intermediate stages between the three types. Thus we find cells like some of those shown in Plate IV., which are like normoblasts except that the nucleus stains pale green or even like a megaloblast. The protoplasm of the normoblast very frequently shows a lesser degree of the degenerative changes supposed to be characteristic of the megaloblast.

The other cells in the plate (*o*, *o*, *o*, etc.) illustrate other of these varieties. A list of those most commonly seen is as follows:[1]

1. Cells like a normoblast, except in showing irregular outline and degenerated protoplasm.
2. Cells like a normoblast, except in having a *pale green* nucleus either small or nearly filling the cell.
3. Combinations of the above.
4. Cells like a normoblast, except that the dark nucleus fills nearly the whole cell.
5. Cells like a normoblast, except that the cell body is as large as that of a megaloblast.
6. Same as 5, but with pale nucleus.
7. Cells like a megaloblast, but having a *dark* nucleus instead of a light one.
8. Cells like a megaloblast, but showing only minute specks of dark nuclear substance scattered through them.
9. Cells like a normoblast with dividing nucleus, but much larger.
10. Cells with mitosis in the nucleus.

Besides the difficulties entailed by the existence of all these unnamed varieties, we have the ambiguity and uncertainty involved in the definition of the named types. For instance, a megaloblast is a cell considerably larger than a normoblast. How much larger? It has a large pale nucleus; how large and how pale?

These questions may seem like quibbling, but when it

[1] I have seen all of these in a single cover-glass specimen, so that the differences do not depend on differences in the methods of preparation and staining.

depends on the answer given to them whether we class a given cell as a megaloblast or as a normoblast, and the prognosis of the case depends on the relative proportions of these two varieties, it may make considerable difference which way we decide.[1]

For reasons given more fully in the chapter on "Pernicious Anæmia," I have usually adopted the following definitions:

Normoblast: A nucleated red cell not over 10 μ in diameter, whose nucleus is not more than one-half the diameter of the cell. The nucleus may be dividing or divided, but must stain deeply.

Megaloblast: All other varieties of nucleated red cells except microblasts.

I think it is evident that there is no sharp line to be drawn between the three types of cells, or the two methods of blood formation, so that these divisions into normoblast, microblast, and megaloblast are somewhat misleading and arbitrary. But they have a certain convenience if used only to mean the extremes of the series, from the most fruitful to the least fruitful kind of nucleated cell.

In secondary anæmia of all kinds we may always find normoblasts. In very severe forms, whatever the cause, we may or may not find an occasional megaloblast. But these are much rarer than the normoblasts, even in the severest types of secondary anæmia. The only exceptions to this rule are the anæmias due to intestinal parasites, in which, though secondary and curable, the megaloblasts in some cases predominate over the normoblasts.

Summing up the changes characteristic of secondary anæmia, which includes almost all the important pathological appearances occurring in red cells, we have:

I.	(*a*) Lack of hæmoglobin. (*b*) Lowered specific gravity.	Characteristic of mild cases.
II.	The above and necrobiotic changes of Maragliano.	Characteristic of moderate cases.
III.	(*a*) Lack of red cells. (*b*) Presence of normoblasts and the above (I. and II.).	Characteristic of severe cases.
IV.	Megaloblasts and the above (I., II., and III.).	Characteristic of very severe cases.

[1] Cf. Askanazy: Zeit. f. klin. Med., 1896, vol. xxvii.

The changes in the white cells will be discussed in the next chapter.

Among the commonest causes of secondary anæmia are: I. Infective and febrile diseases, acute or chronic. II. Malignant disease. III. Chronic suppurations, nephritis, chronic dysentery, cirrhosis of the liver. IV. Bad hygiene, pregnancy, and lactation. V. Intestinal parasites. VI. Poisons (lead, arsenic, etc.).

To discuss the way in which each of these influences acts in producing anæmia is tempting, but falls outside the plan of this book.

2. Hydræmia.

(*a*) Seen from the opposite point of view almost all cases of anæmia are hydræmic. That is, if the total volume of blood is to remain approximately constant (as it appears to do), any loss of solids (corpuscle substance) must be made up by water taken in from the tissues. Hence any anæmic person's blood is thin, watery, or hydræmic. Women's blood is somewhat more hydræmic than men's, because less rich in cells.

(*b*) In many conditions of dropsy, whether from heart or kidney, we may have more water than normal, both in the plasma and in the corpuscles themselves, which are capable of taking up considerably more than their normal amount of water.

(*c*) Any temporary dilution of the blood under the conditions mentioned above (ingestion of liquid, lowered blood pressure, etc.) is from one point of view a hydræmic condition.

No special clinical significance attaches to it other than that of anæmia, whose correlative it is.

CHAPTER VIII.

LEUCOCYTOSIS—LYMPHOCYTOSIS—EOSINOPHILIA—MYELOCYTES.

MUCH confusion has been caused in the past by the failure to see in leukæmic blood anything more than an extreme and permanent form of leucocytosis, while leucocytosis was thought of as a mild and temporary leukæmia.

We know now that they are totally different phenomena, differing not in the number, but in the *kind* of cells present in the increased numbers.

Definition.

There are many difficulties in defining leucocytosis. To my mind the term is best used to mean: *An increase in the number of leucocytes in the peripheral blood over the number normal in the individual case, this increase never involving a diminution in the polymorphonuclear varieties, but generally a marked absolute and relative gain over the number previously present.*

(*a*) I say "in the peripheral blood" because the majority of observers now hold that leucocytosis is not a real increase in the total number of leucocytes in the blood, but only an affair of distribution, the cells being drawn or attracted to the periphery and out of the internal organs. Whether this theory be true or not, it is accurate to say that in the drop which we draw (whether also in the internal organs or not), the leucocytes are present in increased numbers per cubic millimetre.

(*b*) In persons not usually to be considered sick, but simply somewhat wizened or ill-nourished, the normal count of white cells may be as low as three thousand per cubic millimetre. For such an individual ten thousand cells per cubic millimetre would be a decidedly pathological condition. On the other hand, there are persons, usually those of notable vigor and good nutrition, whose white cells rarely fall below ten thousand.

Obviously we must take account of these differences both in our definition and in our practice if we are to reason correctly from the data of blood examination.

(*c*) Further we must lay stress upon the varieties of leucocytes whose increase constitutes leucocytosis in distinction from either variety of leukæmia (splenic-myelogenous, or lymphatic).

For instance, given a count of eighty thousand leucocytes per cubic millimetre, we cannot tell without knowing the varieties of cells present whether the case is a genuine leukæmia or a merely leucocytosis symptomatic of pneumonia, suppuration, malignant disease, or other conditions.

(*d*) Thus defined leucocytosis is of two kinds. 1. That in which the relative proportions of the different varieties to each other is unchanged. 2. That in which the increase is made up solely or largely by a gain in the polymorphonuclear or adult leucocytes.

The latter includes nearly all pathological leucocytoses, the former being confined chiefly to the physiological leucocytoses next to be described.

(*e*) Lastly, in order to be sure that the polymorphonuclear cells are not decreased, we must know what the normal percentage *for that individual* is. The normal percentage of these cells in infancy is from twenty-eight to forty per cent. In adults it is much higher, but varies like the total count, according to conditions of nutrition, etc. Thus the normal for adults is usually set at from sixty to seventy per cent, but no one individual's blood shows such variations in health, and if we include the obviously ill-nourished, but not actually sick, and also those in blooming health, we shall have to widen our normal limits considerably. From fifty to seventy-five per cent are within normal limits according to the above conception. But obviously we can make no absolute judgment by a standard so vague. It is much better, I think, to consider each individual as his own standard within these limits, his count of polymorphonuclear cells being a fair measure of the soundness and vigor of his metabolism. Thus, in an obviously debilitated individual, we should consider seventy-two per cent of these cells very high, while in a vigorous athlete it might not be so.

It is the endeavor to include all these limiting conditions that has made my definition so long and involved. It gives us, if it turns out to be true, some better way of classing individuals than as "sick" or "well" as regards their blood state. We find out *how* well or how sick their blood is (to a certain extent), (*a*)

by the total number of leucocytes present, and (*b*) by the proportion of old cells (polymorphonuclear) in a given one thousand of those leucocytes. These data tell us approximately *how* normal or *how* abnormal a given individual's blood is. When a given disease like pneumonia occurs, we need to know, if possible, what is the ordinary leucocyte count and differential count of that case, on top of which a leucocytosis may (or may not) be built up.

Condition of stasis, temporary blood concentration, dilution, and vasomotor disturbances must, of course, be excluded or allowed for, since these may increase not only the total leucocyte count, but often the percentage of adult cells. Whether or not differences of race make any difference in the normal count of white cells, I cannot say, but certainly the average of a group of college athletes would be higher than that of some country towns in New England where everybody is more or less under-nourished; and if one is to practise among all sorts and conditions of men, I think he cannot but expect to find people's leucocytes vary all the way *from 3,000 to 10,500 per cubic millimetre*, without there being anything more than malnutrition to account for the lower figures.

Into the theories of how leucocytosis is brought about I shall not enter; no one of them as yet commands general assent.

We may divide leucocytoses for convenience' sake into: 1. Physiological leucocytoses. 2. Pathological leucocytoses.

Physiological Leucocytoses.

1. Leucocytosis of the new-born.
2. Leucocytosis of digestion.
3. Leucocytosis of pregnancy.
4. Leucocytosis of post-partum.
5. Leucocytosis after violent exercise, massage, and cold baths.
6. Leucocytosis of the moribund state.

The Leucocytosis as Affected by Digestion.

(*a*) Total abstinence from food lowers the leucocyte count. In the blood of the professional faster Succi, the number sank within his first week's fast to 861 per cubic millimetre. After

the first week it rose to 1,530, and remained there throughout his thirty days' abstinence (Luciani [1]).

Von Limbeck counted the blood of a melancholic patient who had fasted a week, and found 2,800 white cells per cubic millimetre. These facts support the idea that the number of leucocytes depends (within certain limits) on the individual's assimilation of food. In cancer of the gullet we find similar low figures.

(*b*) After a meal rich in proteids the leucocyte count rises about thirty-three per cent in most sound persons. Ten thousand cells may perhaps be considered the average, three to four hours after a proteid meal, but if the count before a meal is only 4,000 or 5,000, digestion will perhaps not raise it above 7,000, while vigorous adults may show 13,000. Digestion leucocytosis is always *relative* to the count of the individual's blood *when fasting*. This is to be obtained preferably before breakfast, as during the day the leucocytosis caused by one meal may not be gone before the influence of the next meal begins.

Occasionally we see sound persons with little or no digestive leucocytosis. Some of these cases are to be explained by habitual constipation (v. Limbeck); in others the reason is more obscure. But there is no doubt of its being the rule after meals of mixed or proteid diet. In herbivorous animals, and presumably in vegetarians, it is not found.

Any disease of the gastro-intestinal tract, whether functional or organic, may prevent the appearance of the digestion leucocytosis (see later under Diseases of the stomach, page 241). In anæmic and debilitated conditions it is frequently absent.

In children it is especially marked. Schiff [2] records a case of a healthy infant whose blood an hour after birth showed 19,500 (see next section), after its first meal 27,625, and after its fourth meal 36,000 white cells per cubic millimetre. After the second day this gradually diminished.

Food seems to call forth a greater leucocytosis in proportion as it is a *novelty* in the stomach. Cases of gastric ulcer who had been fed exclusively by rectum for some weeks show a greater leucocytosis after their first meal than later. Perhaps the size of the digestion leucocytosis in the new-born is to be

[1] "Des Hungern," German translation by O. Fränkel. Hamburg, 1890.
[2] Zeit. f. Heilk., xi., 1890.

similarly explained. In diabetics the digestion leucocytosis is sometimes very large.

The leucocytosis can usually be observed one hour after a meal, increases for two, three, or even five hours according to the slowness of digestion, then falls again.

Excepting the eosinophiles, the proportion of the different varieties of leucocytes to each other is not considerably affected, this being one of the few varieties of leucocytosis in which the increase takes place "all along the line," without special predominance of any single variety. In other words, the blood is neither older nor younger. The eosinophiles, however, are markedly diminished.

Diagnostic Value.

1. When we wish to know whether a person is accurate in such statements as that they have "eaten nothing for a week," we can get evidence from the leucocyte count, which should be very low if the assertion be true. Whenever we cannot communicate with a patient and wish to know how much food he has taken of late, we can form some idea from the blood examination. In the case of a patient who spoke only Russian, I was led to look for a stenosis of the gullet by the lowness of the leucocyte count (2,700), and the probang confirmed the suspicion.

2. As suggested above, we can form some idea of a person's general vigor, nutrition, and capacity to assimilate food by the number of leucocytes and the proportion of mononuclear (young) cells, as compared with the average figures for that age and locality. Persons *debilitated* from any reason are apt to show it in their blood by the changes above mentioned, the element of hysteria being sometimes recognizable by other signs (see below: "Eosinophilia," page 101).

3. Slowness of digestion is indicated by a late appearance of the digestion leucocytosis. The inferences to be drawn from the blood in diseases of the gastro-intestinal tract will be discussed later (page 236).

4. Perhaps the chief importance of digestion leucocytosis is as a possible cause of false inferences, through being taken for a pathological increase. Bearing this in mind, we must always examine the blood as *near* a meal as possible, or better still before breakfast.

Leucocytosis of the New-Born.

The following table is compiled from the best authorities on the subject (Schiff, Gundobin, Bayer, Hayem, and others):

Age.	Red cells.	Leucocytes.
At birth	5,900,000	17,000 to 21,000 (26,-000 to 36,000 after first feeding).
End of first day	7,000,000 to 8,800,000	24,000
" second day	Generally increased.	30,000
" fourth day	6,000,000	20,000
" seventh day	5,000,000	15,000
Tenth day	....	10,000 to 14,000
Twelfth to eighteenth day	....	12,000
Sixth month	....	12,000
Sixth year and upward	....	7,500

The increase is explained by Lepine, v. Limbeck, and others as a combination of blood concentration with large digestion leucocytosis. Gundobin and others are opposed to this theory. Certainly the influence of digestion on infant's blood is much greater than in adults. After a meal 30,000 leucocytes is never a very high count in infants under two years.

A fuller discussion of the subject will be found in the chapter on the blood in infancy.

The Leucocytosis of Pregnancy.

Most primiparæ show during the latter months of pregnancy a moderate increase of all varieties of leucocytes. Thirteen thousand cells per cubic centimetre is about the average count.

In multiparæ it occurs in only about fifty per cent of the cases. Digestion leucocytosis "on top of" the constant pregnancy leucocytosis, so to speak, does not occur.

As mentioned above, the relative percentage of the different types of leucocyte *remains unchanged,* so that all varieties must be equally increased (eosinophiles excepted). The fact that digestion does not increase the pregnancy leucocytosis, leads to the suggestion that the whole thing may be only a prolonged digestion leucocytosis—the mother having to eat for two. The swelling of the breasts may also account for part of the leuco-

cytosis. In the last weeks of pregnancy the leucocytosis increases till at the beginning of labor it is often 16,000 to 18,000. It has no diagnostic value, as it is not present during the earlier months of pregnancy when diagnosis is difficult, and in the later months such conditions as hydatiform mole and fibroid tumors might raise the count of white cells as much as pregnancy.

Leucocytosis After Parturition.

The following charts illustrate the course of the leucocyte curve from the time of parturition till the end of the second week after it.

All were primiparæ excepting Nos. 5, 8, and 9. There was no sepsis in any case, and the temperature charts were practically normal after the second day. No reasons are known for the variations between the different cases. All were counted at the same hour of the day, and under the same conditions of nutrition. All nursed their children.

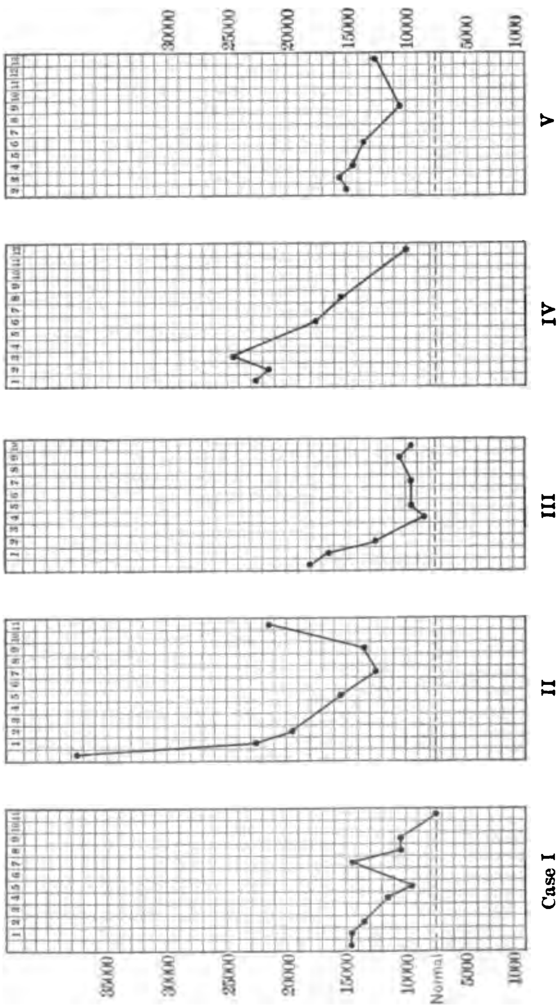
The only importance of this leucocytosis is that it might be confounded with a pathological leucocytosis in a case suspected of being septic. Just how long the leucocytosis is prolonged during lactation has not been studied so far as I am aware, but it certainly may go on several weeks.

Violent exercise, massage, and short cold baths have been shown to cause a temporary increase in the number of leucocytes in the peripheral blood, all varieties of the cell being equally increased. The explanation usually given is that the blood is concentrated by vasomotor contraction and rise of blood pressure.

Schultz (*Deut. Arch. f. klin. Med.*, 1893, page 234) found the *leucocytosis of exercise* amount to about the same as that of digestion, 11,000 to 13,000. He also noted that in dogs merely opening the peritoneum aseptically or breaking a leg caused leucocytosis.

Thayer studied twenty cases of typhoid and found an average of 7,724 white cells before and 13,170 after a Brand bath (*Johns Hopkins Medical Bulletin*, April, 1893). The increase took place equally in all varieties. Winternitz (Imperio-Royal Medical Society, Vienna, February, 1893) came to a similar conclusion and found also that prolonged cold bathing decreased

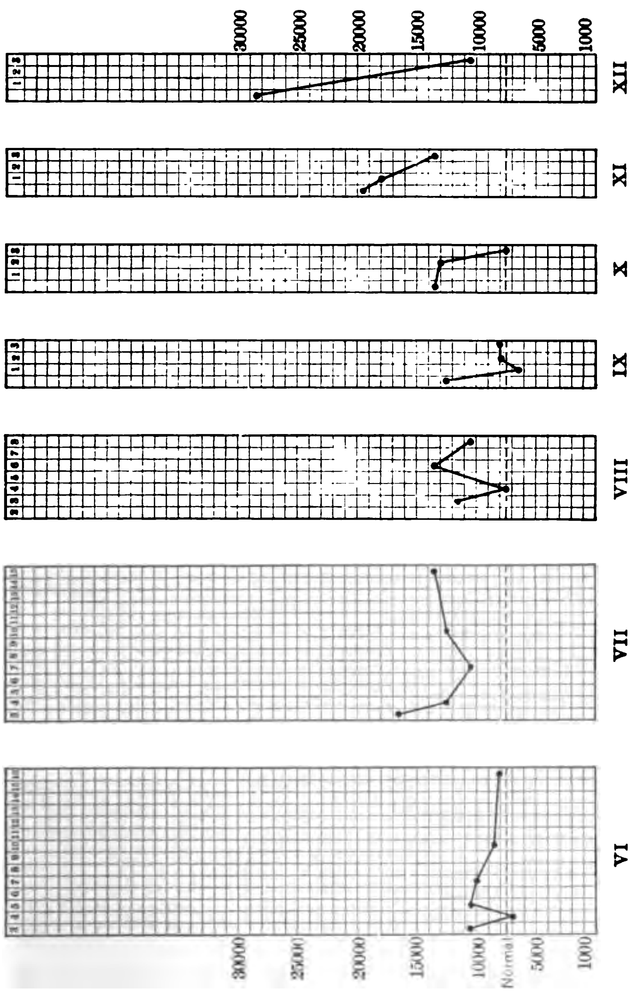
the number of white cells (dry cold does the same). On the contrary, short hot baths decrease and prolonged ones increase the number of leucocytes.



The numbers at the top of each chart indicate the days *post partum*. Those at the side mean the number of leucocytes per cubic millimetre.

Local arm baths have a similar effect, raising the count of leucocytes in the blood of the immersed arm if cold and short, and lowering it if hot and short, while prolonged immersion has an

opposite effect. In the other arm the counts go up when those of the immersed arm go down, and *vice versa* (Rovighi).[1] Mitchell[2] found that the leucocytes showed distinct increase (as well as the red cells and hæmoglobin) after one hour's general massage.



The numbers at the top of each chart indicate the days *post partum*. Those at the side mean the number of leucocytes per cubic millimetre

All these forms of leucocytosis are usually explained by changes in blood pressure, and vasomotor changes affecting the

[1] Arch. Ital. d. Clin. Med., xxxii., 3, 1893.
[2] American Journal of the Medical Sciences, May, 1894.

calibre of the peripheral vessels and consequently their contents.

Terminal Leucocytosis.

The leucocytosis of the moribund state, though by no means invariable, occurs in many cases, whether from the influence of a terminal infection or from stasis. Where death is sudden or rapid it does not occur. It seems to be analogous to the terminal rise of temperature seen at the close of many chronic non-febrile affections. The longer the patient is moribund the higher the count reaches. In pernicious anæmia the increase may be so great as to simulate lymphatic leukæmia. Such a case occurred in the writer's own experience. The patient had presented the signs and symptoms of pernicious anæmia, and the blood was typical of the disease in all respects except for the lack of nucleated red cells.

Slides taken on the day of death showed a ratio of one white to fifteen red cells, the small lymphocytes greatly predominating, but the autopsy revealed simply the lesions of pernicious anæmia. The differential count of one thousand leucocytes on the day of death showed: Young cells, 91.7 per cent; adult cells, 7.7 per cent; old cells, 0.5 per cent. Four megaloblasts were seen while counting these. The total leucocyte count was unfortunately not made.

In ordinary cases the differential count shows an increase in the adult leucocytes. Thus in a case reported by Rieder, in which the leucocyte count rose during the last two days of life from 7,800 to 59,300, the polymorphonuclear cells constituted 87.5 per cent of the whole 59,300.

Pathological Leucocytoses.

For convenience' sake these may be divided as follows:

1. Post-hemorrhagic leucocytosis.
2. Inflammatory leucocytosis.
3. Toxic leucocytosis.
4. Leucocytosis in malignant disease.
5. Leucocytosis due to therapeutic and experimental influences.

1. *Post-hemorrhagic Leucocytosis.*

Within an hour after a large hemorrhage we find commonly a considerable increase (16,000–18,000). In hemorrhage from the stomach this disappears again usually within a day or two, while in ordinary traumatic hemorrhage it persists longer. This last fact may perhaps be explained, as v. Limbeck suggests, by the local conditions in the wound rather than by the loss of blood in itself.

The adult leucocytes are increased relatively and absolutely as in other forms of pathological leucocytosis. The degree of increase in the white cells is parallel in a general way to the anæmia produced in the individual, *i.e.*, it depends on his powers of recuperation rather than on the amount of blood lost. Its duration follows the same rule.[1]

2. *Inflammatory Leucocytosis.*

I use the term "inflammatory leucocytosis" rather than "leucocytosis of infectious diseases" because there is a considerable number of infectious diseases in which no leucocytosis occurs, while it accompanies almost all forms and cases of inflammation. Nevertheless I shall class under this heading some diseases in which inflammation plays but a very subordinate rôle.

I. Although *purulent and gangrenous* processes usually cause a higher count of white cells than *serous* processes, the amount of the exudation is not a measure of the amount of leucocytosis. It seems to depend rather on the resultant of two forces, viz., the severity of the infection and the resisting power of the individual. These factors may interact in various ways:

1.	Infection	mild:	resistance	good	= small leucocytosis.
2.	"	less mild:	"	less good	= moderate leucocytosis.
3.	"	severe:	"	good	= very marked leucocytosis.
4.	"	"	"	poor	= no leucocytosis.

This will be illustrated later under "Pneumonia" and under "Sepsis." Experiments on animals show that whereas moderate sized doses of septic cultures, not sufficient to kill the

[1] Further account of the blood after hemorrhage will be found on page 109 et seq.

animal, are followed by leucocytosis, larger doses after which death follows speedily, do not raise the leucocyte count at all. Animals weakened by any cause show less leucocytosis to a moderate dose than strong animals.

If the individual reacts from the shock his leucocytes are increased again and rise above normal. If reaction fails the leucocytes do not rise.

II. Inflammatory leucocytoses differ from physiological leucocytoses—

(*a*) In being usually of larger extent.

(*b*) In being accompanied by a relative and absolute increase in the percentage of polymorphonuclear (adult) cells.

III. The course of the leucocytosis as regards both amount and duration shows, like the temperature chart, certain more or less characteristic differences in different diseases.

IV. In some cases in which the absolute number of leucocytes is not increased, we see a relative increase in the adult cells, pointing to the fact that influences are at work similar to those which produce an *absolute* increase.

V. That the amount of exudation is not of itself a measure of the amount of leucocytosis is shown by the fact that erysipelas or scarlet fever may be accompanied by as high a count as the average count in pneumonia or empyema.

That purulent exudations usually have more effect on the white cells than do serous ones is due, I suppose, to the fact that a purulent inflammation usually means a severer infection.

VI. No direct connection exists between leucocytosis and fever, many febrile affections running their course with a normal leucocyte count. When both leucocytosis and fever are due to the same causes they rise and fall together, but the correspondence is rarely accurate, and marked leucocytosis may exist without fever.

VII. Acute, rapidly spreading inflammations seem to produce a greater leucocytosis (other things being equal) than those in which the process is relatively chronic and stationary. For instance, an appendicitis, when well walled off and stationary, shows less increase in white blood cells than while its lesions are progressing. But peracute, overwhelming general sepsis may have no effect on the leucocytes, the reactive power of the organism being crushed.

VIII. Most inflammatory leucocytoses are preceded by a temporary diminution in the number of leucocytes. This occurs in animals from *shock* of any kind (blows on the head, tying to the etherizing board), and it seems not unlikely that the cause is the same in all cases.

The following is a list of the more important inflammatory or infectious conditions in which leucocytosis appears:

1. *Infectious diseases with comparatively slight local inflammatory processes:*

(*a*) Asiatic cholera.

(*b*) Relapsing fever.

(*c*) Typhus fever (according to the majority of observers).

(*d*) Scarlet fever.

(*e*) Diphtheria and follicular tonsillitis.

(*f*) Syphilis (secondary stage).

(*g*) Erysipelas.

(*h*) The bubonic plague.

2. *Infectious diseases with more extensive local lesions:*

(*a*) Pneumonia.

(*b*) Small-pox (suppurative stage).

(*c*) Malignant endocarditis, puerperal septicæmia, and all pyæmic and septicæmic conditions.

(*d*) Actinomycosis.

(*e*) Trichinosis.

(*f*) Glanders.

(*g*) Acute multiple neuritis and beri-beri.

(*h*) Acute articular rheumatism.

(*i*) Septic meningitis and cerebro-spinal meningitis.

(*j*) Cholangitis, cholecystitis, and empyema of the gall bladder.

(*k*) Acute pancreatitis.

(*l*) Endometritis, cystitis (some acute cases).

(*m*) Gonorrhœa.

3. *Local inflammatory processes:*

(*a*) *Abscesses* of all kinds and situations, such as

Felon.

Carbuncle, furunculosis.

Tonsillar and retropharyngeal abscess.

Appendicitis.

Pyonephrosis, perinephritic abscess and pyelonephritis.

7

Osteomyelitis.

Psoas and hip abscess when not simply tubercular.

Abscess of lung, liver, spleen, ovary, prostate.

Salpingitis and pelvic peritonitis.

(*b*) *Inflammations of the serous membranes* including:

Pericarditis, peritonitis, pleurisy, arthritis (serous or purulent, non-tubercular).

(*c*) *Gangrenous inflammations*, as of the

Appendix, lung, bowel, mouth (noma).

(*d*) Many inflammatory skin diseases, such as dermatitis, pemphigus, pellagra, herpes zoster, prurigo, some cases of universal eczema, etc.

3. *Toxic Leucocytosis.*

Under this heading I have grouped most of the conditions not obviously to be explained as infectious or inflammatory (though some may turn out to be such) and not due to malignant disease or therapeutic agencies. This classification is chiefly for convenience' sake and represents only a guess at the real explanation of the leucocytosis:

(*a*) Leucocytosis of illuminating-gas poisoning.
(*b*) " " quinine poisoning.
(*c*) " " rickets (many cases).
(*d*) " " the uric-acid diathesis, gout.
(*e*) " " acute yellow atrophy of the liver.
(*f*) " " advanced cirrhosis of the liver (some cases) especially with jaundice.
(*g*) " " acute gastro-intestinal disorders (ptomains ?).
(*h*) " " acute nephritis, and some chronic cases, usually uræmic.
(*i*) " " hydronephrosis.
(*j*) " after injections of tuberculin and thyroid extract.
(*k*) " after injection of normal salt solution (intravenous).
(*l*) " after ingestion of salicylates.
(*m*) " during and after etherization.

Possibly the leucocytosis of *acute delirium* belongs also in this group.

4. *Leucocytosis of Malignant Disease.*

Very likely this belongs more properly under one or another of the classes just mentioned. Some observers think that it occurs only from the inflammation excited in the periphery of some malignant tumors; others that it is due to absorption of morbid products from the tumor itself; others again that it is to be accounted for by the cachectic state associated with the growth of the tumors. The details and conditions of its occurrence will be discussed later (page 287).

5. *Leucocytosis Due to Therapeutic and Experimental Influences.*

Pohl[1] found that most of the so-called tonics and stomachics produce a slight increase in the white cells in animals, particularly the vegetable tonics like tincture of gentian, and oil of anise seed, while bismuth, bicarbonate of soda, and iron had no such effect. Quinine, caffeine, and ethyl alcohol gave likewise negative results. Von Limbeck found leucocytosis in men after oil of peppermint and oil of anise seed.

Binz[2] got the same results with camphor. In all these experiments the substances were given by the mouth.

Using subcutaneous or intravenous injections, Löwit experimented on animals with hemialbumose, peptone, pepsin, nucleinic acid, nuclein, extract of blood-leech, pyocyanin, tuberculin, curare, uric acid, urate of sodium, and urea. All but the last of these produce temporary decrease followed by increase of leucocytes.

Goldschneider and Jacob[3] used extracts of various organs. Extract of spleen, marrow, and thymus produced leucocytosis preceded, as in Löwit's experiments, by a brief diminution in the number of leucocytes, while extract of pancreas, thyroid, kidney, and liver had no effect.

Winternitz[4] injected a large variety of substances subcutaneously and found that the degree of leucocytosis was parallel to the degree of local reaction excited.

For example, neutral salts and weak acids or alkalies pro-

[1] Arch. f. exp. Path. u. Pharm., 1889, vol. xv.

[2] Arch. f. exp. Path. u. Pharm., vol. v., p. 122.

[3] Arch. f. Anat. u. Physiol., 1893, p. 567.

[4] Arch. f. exp. Path. u. Pharm., vol. xxxv., p. 77.

duced slight local inflammation and a leucocytosis of from forty to seventy-five per cent of the original count. But irritants like turpentine, croton oil, nitrate of silver, sulphate of copper, mercury, antimony, digitoxin, etc., produced local suppuration (aseptic) and much greater leucocytosis (two hundred to three hundred per cent).

Pilocarpine and antipyrin have been found by v. Jaksch and others to produce marked increase in the number of leucocytes when given subcutaneously. During the use of thyroid extract Richter (*Centralblatt f. inn. Med.*, 1896, p. 3) noted leucocytosis.

A large number of observations on the effects of injections of bacteria or their toxins agree in the following results.

1. Where the dose is very large the leucocytes are reduced, and the animal dies.
2. Where the dose is not sufficient to kill the animal the temporary diminution in the leucocytes is soon followed by leucocytosis.
3. Where the dose is slowly fatal the count of leucocytes oscillates up and down within wide limits.
4. Animals previously rendered immune to the poison injected show little or no leucocytosis.
5. Leucocytosis is more easily called forth and of greater extent in young animals.
6. Most pathogenic organisms act similarly, but bacilli and toxins of tuberculosis as a rule cause no leucocytosis.
7. There is no evidence that any one variety of leucocyte is attracted by any particular bacillus or toxin.

In the above sketch of therapeutic and experimental forms of leucocytosis no attempt has been made to give anything but the more interesting and important outlines of the immense amount of work done.

Absence of Leucocytosis.

It is of fully as great a practical assistance to us to know that in certain infective diseases leucocytosis is regularly absent as to know those conditions in which it is to be expected. Among the most important diseases in which leucocytosis is conspicuously absent are:

(*a*) Typhoid fever.

(*b*) Malaria.
(*c*) Grippe (most cases).
(*d*) Measles.
(*e*) Rötheln.
(*f*) Tuberculosis, including—
Incipient phthisis.
Miliary tuberculosis.
Tubercular meningitis.[1]
" peritonitis.
" ostitis and periostitis.
" pleurisy.
" pericarditis.

In some of these affections, notably in miliary tubercle and the later weeks of typhoid, the leucocytes are diminished. Further details will be given under the special diseases.

Leucopenia.

Definition.—A diminution in the number of white cells in the peripheral circulation as compared with the number normal for the given individual.

1. The effects of starvation and malnutrition in producing leucopenia have already been described. Such leucopenia is usually associated with lymphocytosis (see below). Cancer of the gullet is an example of this class.

2. Short hot baths or prolonged cold baths produce temporarily the same result (Winternitz, *loc. cit.*).

3. Most of the infective diseases in which there is no leucocytosis are sometimes characterized by leucopenia, *e.g.*, grippe, measles, miliary tuberculosis, and other forms of pure tubercular infection, malaria, and especially typhoid, in the later weeks of which it is almost invariable, and is accompanied by lymphocytosis.

Where a case of leukæmia is complicated by an infective disease (pneumonia, septicæmia) the number of leucocytes may fall below the normal. In a case recently occurring at the Massachusetts General Hospital in which a lymphatic leukæmia was terminated by septicæmia from glandular suppuration, the

[1] Osler in the last edition of his text-book records that leucocytosis *is* often present in this disease. Most other observers have not found it.

white cells fell gradually from 40,000 three weeks before death to 419 per cubic millimetre on the day of death. I have never heard of a lower count than this. The differential count was unchanged (lymphocytes = ninety-eight per cent).

4. In pernicious anæmia the count is usually very low and may fall below 1,000 cells per cubic millimetre. Other forms of anæmia (rachitic, syphilitic) occasionally produce the same result.

LYMPHOCYTOSIS.

Lymphocytosis is a relative increase in the lymphocytes or young cells in the blood, with or without an increase of the total leucocyte count. The increase is relative to the percentage of young cells normal for the individual. When lymphocytosis and an increase of the total leucocyte count are present we cannot distinguish the blood from that of lymphatic leukæmia, and the distinction must depend upon the course and symptoms of the case.[1]

1. Such a condition (relative to the adult) occurs *in healthy infant's blood* and in many diseases of infancy, the blood seeming to have a tendency to return to the infantile type. Anything that retards the infant's normal gain in weight or general development retards its blood development as well. Thus a child of three, convalescent from a summer diarrhœa, may have fifty to sixty per cent of young leucocytes which would be normal for an infant of a few weeks, but for three years old is very high.

2. *Rickets* and *hereditary syphilis* are perhaps the best known causes of relative lymphocytosis in children. *Scurvy* may produce the same result. Dividing the anæmias of children into two groups, those that do and those that do not produce leucocytosis, it appears that the great majority of those whose total leucocyte count is normal show a relative lymphocytosis. This is the case irrespective of whether there is enlargement of the spleen or not.

Sometimes the smaller, sometimes the larger lymphocytes are in the majority. Often no division between the two kinds is possible.

[1] The lymphocytosis of chlorosis has been mistaken for lymphatic leukæmia (Schreiber) owing to too exclusive reliance on the results of the blood examination. The patient recovered.

3. In adults some forms of *debility* may be associated with relative lymphocytosis as above noted (page 82). It is most marked, however, *in chlorosis, pernicious anæmia,* and the anæmia secondary to *syphilis*, in the later weeks of typhoid fever and in lactation.

4. Certain cases of *Graves' disease* show marked lymphocytosis. How such cases differ from those that do not show it I have not been able to determine.

5. It occurs also in *hæmophilia, goitr* , in some cases of *cervical adenitis*, whether tubercular or lymphomatous, and in *tumors of the spleen.*

6. During the administration of thyroid extract a lymphocytosis has been recently noted by Perry (New York *Medical Rec-Record*, August 29th, 1896).

7. The larger forms of lymphocytes are increased in some splenic tumors (chronic "ague cake"), at the end of scarlet fever, in pneumonia with delayed resolution (some cases), in measles, certain forms of phthisis and in the non-suppurative stages of small-pox; also in many of the same diseases in which the small lymphocytes are increased.

8. So far I have referred chiefly to relative lymphocytosis. Absolute lymphocytosis is very rare outside of lymphatic leukæmia. One case occurred at the Massachusetts General Hospital in 1894—a child of six, who passed through an attack of bronchopneumonia with uneventful recovery, the only peculiarity of the case being the marked increase of white cells running up to 94,600, *sixty-nine per cent of which were lymphocytes.* During convalescence the blood became normal and the child left the hospital well in all respects. The case will be referred to later in the account of the blood of pneumonia.

Diagnostic Value of Lymphocytosis.

1. I have already suggested that the degree of health in persons not organically diseased might perhaps prove to vary directly with the percentage of adult cells in the blood.

2. In children the same percentage is to a certain extent a measure of the child's degree of development—causes of leucocytosis being excluded, and the percentage normal for a child of the patient's age being taken as the standard.

3. The diagnosis of obscure syphilitic disease may be supported by the coincidence of lymphocytosis with eosinophilia.

4. Absolute lymphocytosis in the presence of glandular tumors is our mainstay in the diagnosis of lymphatic leukæmia.

EOSINOPHILIA.

Definition.—An increase in the percentage of eosinophiles in the circulatory blood, with or without an increase in the total leucocyte count.

The researches of Neusser, Zappert, Weiss, Klein, and others have brought the eosinophilic cells once more into the prominence which they lost when it became apparent that they were in no way peculiar to leukæmia.

1. Leukæmia is occasionally associated with eosinophilia (see below, page 146), but in the majority of cases this is not so. As in normal blood, from one to three per cent of them are to be found.

2. In infancy the percentage of eosinophiles is very often higher than in adults, so that in them eosinophilia may be considered physiological. In adults its presence is often unexplained. The eosinophiles are the most seemingly capricious of all blood cells. A certain amount of light has been thrown on them by the observations of Neusser and his pupils (Weiss, Schreiber, Klein, and others).

3. Neusser noticed that eosinophilia occurs—

(A) In many affections of the bones (sarcoma, leukæmia, osteomalacia).

(B) In many affections of the skin (pemphigus, pellagra, and others).

(C) In troubles involving the female genitals, especially the ovaries.

(D) In disturbances of the sympathetic nervous system.

That there is some relation between these seemingly unconnected sets of phenomena is shown by various *other* facts besides the presence of eosinophilia in them all.

(*a*) Bone and genitals.

Osteomalacia is most apt to occur in pregnancy and is cured in some cases by castration.

(*b*) Genitals and sympathetic nervous system.

The presence of all sorts of psychoses and vasomotor troubles associated with menstruation, pregnancy, and the climacteric, and the so-called "reflex" disturbances in connection with uterine or ovarian disease, are well known.

(*c*) The connection of the skin with both of the last-mentioned systems is seen in the trophic disorders and sympathetic dermatoses of hysteria and ovarian disease.

Working out the suggestions of this theory Neusser and his pupils have found relative eosinophilia in the following affections:

1. *Bones.*

Osteomalacia, malignant bone-tumors, pernicious anæmia (some cases), splenic-myelogenous leukæmia (occasionally). [The writer has seen slight eosinophilia in osteomyelitis.] Possibly the relative eosinophilia of normal infants' blood may be connected with the great activity of their bone growth.

2. *Diseases affecting the skin.*

Urticaria, pellagra, dermatitis herpetiformis, and pemphigus (constantly); some varieties of herpes, prurigo, eczema, lymphodermia perniciosa; the exanthems of scarlet fever and syphilis (*not* measles or small-pox), ichthyosis, lupus, myxœdema.

3. *Genitals.*

Gonorrhœa, prostatitis, many ovarian tumors, before and during the early days of menstruation, puerperal mania, and the psychoses of menstruation, of the puerperium, and of the climacteric; in sexual neurasthenia, after coitus, and in lactation.

4. *Sympathetic Nervous System.*—The psychoses last mentioned, hysteria, Basedow's disease, and some of those given under the next heading.

5. Besides these general groups, Neusser has noticed another class of cases characterized by eosinophilia, namely, those in which some member of the group of *xanthin bases* is supposed to be in the system. In the so-called uric-acid diathesis the nuclein derivatives are transformed in the intestine into one of the xanthin bases, and their presence in the system appears to give rise to eosinophilia.

At any rate we regularly find eosinophilia (according to Neusser) in diseases thought to be characterized by an excess of

these substances in the system. Examples of this are found in gout, bronchial asthma, emphysema, certain forms of migraine and epilepsy, oxaluria, uræmia, tetanus, some gastro-intestinal troubles, ankylostomiasis, after injections of nuclein, pilocarpine, tuberculin, and in most non-malignant liver diseases. All these Neusser believes stimulate the sympathetic nervous system and hence the bone marrow, through the production of xanthin bases. In asthmatic patients he succeeded in producing a paroxysm by injecting nuclein subcutaneously.

Possibly under this heading comes the eosinophilia after antipyrin, and that sometimes found in chlorosis, scurvy, chronic malaria, and phthisical patients with cavities. In the latter cases it has been suggested that the patients may inoculate themselves with tuberculin absorbed from their lung cavities.

6. *Tumors of the spleen* are also accompanied by eosinophilia in some cases. Neusser does not explain this under the theory above sketched.

Many acute mental troubles show eosinophilia, while chronic cases do not.

Other causes of eosinophilia are phosphorus poisoning and. injections of campherin.

In Osler's clinic there has recently been observed and reported a case of trichinosis in which the eosinophilic cells were from the first increased, and continued to increase till at the time of death there was 64 per cent of eosinophiles in a leucocytosis of 25,000.

We also find eosinophilia in many forms of syphilis and syphilitic disease of the spinal cord (tabes dorsalis).

Diminution in Eosinophiles.

1. During digestion.
2. After castration.
3. In febrile stages of pneumonia, grippe, typhoid, diphtheria, sepsis, and most infectious diseases accompanied by leucocytosis. That this is not due simply to the presence of fever is shown by the fact that in malaria and scarlet fever, despite high fever, eosinophiles may be increased.

In the post-critical stages of pneumonia and other infectious diseases the eosinophiles swing up above the normal.

4. Malignant disease, hemorrhage, and most of other causes of leucocytosis also diminish the eosinophiles.

Diagnostic and Prognostic Value of Eosinophilia.

Neusser has suggested the following points:

1. In the diagnosis between puerperal mania and puerperal sepsis, eosinophilia points to the former.
2. Between a tumor connected with the genital system and one not so connected, eosinophilia points to the former.
3. In determining whether a given case of hysteria, neurosis, or psychosis is likely to be benefited by castration, the presence of eosinophilia favors the operation.
4. In malignant disease an eosinophilia points to a metastasis in the osseous system (tumors of the spleen are not included in this rule).
5. In cases of doubtful syphilis eosinophilia combined with lymphocytosis (see above) speaks in favor of syphilis.
6. The diagnosis of any obscure form of "uric-acid diathesis" is helped by finding an increase of eosinophiles.
7. In distinguishing malignant liver disease from other liver disease eosinophilia points to the latter.

1. In the *prognosis* of chlorosis, eosinophilia is favorable.
2. In the prognosis of scarlet fever and scarlatinal nephritis the greater the eosinophilia the better the prognosis.
3. After hemorrhage increased eosinophiles show active regeneration of blood and good prognosis.
4. In pernicious anæmia eosinophilia is favorable for the same reason.

MYELOCYTES.

The occurrence of the myelocyte of Ehrlich in the circulating blood is always to be looked upon as pathological, that is, as the intrusion of a variety of leucocyte naturally a stranger to the circulating blood and a permanent inhabitant of the marrow. Although it is so close morphologically to other varieties of leucocytes that we should certainly suppose it to be an intermediate stage between the large lymphocytes and the polymorphonuclear neutrophiles, the fact that it does not occur outside the marrow in health speaks against the supposition.

Of the occurrence of the myelocyte in leukæmia and pernicious anæmia mention will be made under those diseases. The object of this section is to give a list of the other conditions under which it appears.

Neusser[1] has found small percentages of myelocytes in uræmia, carbonic-acid poisoning, diabetes, syphilis, puerperal mania, osteomalacia, Basedow's disease, and sarcoma, also during menstruation.

Capps found considerable percentages near death in general paralysis (see Book II., page 272).

J. J. Thomas found them in myxœdema.

The majority of other references to them in literature relate to different forms of grave anæmia. For example:

(1) Hayem[2] speaks of cells apparently myelocytes (he did not use Ehrlich's methods) in cases of extreme anæmia.

(2) E. Krebs[3] found them in severe anæmia.

(3) Loos[4] describes them in the anæmia of hereditary syphilis, and Rille[5] finds them in the anæmia of acquired syphilis.

(4) Neusser[6] mentions their presence both in pernicious anæmia and in chlorosis.

(5) Hammerschlag[7] made a similar observation.

(6) Engel[8] noted their presence in a case of what he cautiously calls "pseudo-pernicious anæmia."

(7) Arnold[9] mentions them.

(8) Klein[10] gives a list of various diseases (besides leukæmia), in which they have been found, many of which are essentially anæmic conditions.

(9) Holmes[11] has found them in phthisis. I can confirm this observation.

[1] Cited in Klein: Volkmann's "Samml. klin. Vorträge," December, 1893.

[2] "Du Sang," Paris, 1889, p. 382.

[3] Inaug. Dissert., Berlin, 1892.

[4] Wien. klin. Woch., 1892, p. 291.

[5] *Loc. cit.*, 1893, No. 9.

[6] *Loc. cit.*, 1892, No. 42.

[7] Berlin klin. Woch., August 20th, 1894.

[8] Virchow's Archiv, vol. cxxxv.

[9] *Loc. cit.*, vol. cxl.

[10] Volkmann's "Sammlung klin. Vorträge," December, 1893.

[11] New York Medical Record, September 5th, 1896.

(10) The writer[1] found them especially in the anæmia secondary to malignant disease (see page 305).

Beside these conditions the writer has found them in

	Cases.
Burns (large surface),	2
Osteomyelitis,	2
Malaria, with anæmia,	1
Cystitis and chronic starvation,	1
Septicæmia,	3
Bone tuberculosis,	1
Rickets,	1
Hodgkin's disease,	2
Addison's disease,	1

The most curious example of their occurrence known to me is the following:

Mrs. W—— had been starving herself more or less for six months from motives of economy. Two weeks before I first saw her she began to suffer with cystitis. From both these troubles she made a rapid recovery, which has persisted now eighteen months. There was at the first count a leucocytosis of 15,100; partly due to cyanosis, as she had just been having a chill. The red cells were 7,300,000. Hæmoglobin, eighty-seven per cent. Differential counts were as follows:

Date. Number of cells counted.	May 2d 800. Per cent.	May 6th 1,000. Per cent.	May 7th 400. Per cent.	May 8th 400. Per cent.	May 13th 1,000. Per cent.
"Polynuclear neutrophiles"	82.7	82.2	83.6	80.2	68.5
Lymphocytes	8.6	12.5	9.4	11.3	25.2
Large mononuclear	8.2	1.5	2.0	6.0	5.2
Myelocytes	.5	3.5	4.0	2.5	.6
Eosinophiles	.0	.3	1.0	.0	.5

What caused the presence of myelocytes I do not know. At that time I had never seen them in any curable disease and was alarmed by their appearing, but this case proves that they are not always of any importance.

In a general way their presence seems to have about the same significance as that of normoblasts.

[1] Boston Medical and Surgical Journal, *loc. cit.*

CHAPTER IX.

GENERAL PATHOLOGY OF THE BLOOD AS REGARDS HÆMOGLOBIN, FIBRIN, LIPÆMIA, MELANÆMIA AND HEMORRHAGE.

HÆMOGLOBIN.

As stated above, the hæmoglobin may increase and diminish in lines parallel to those of the red cells. In that case we suppose the amount of hæmoglobin per corpuscle to be normal and the *color index* or *valeur globulaire* is said to = 1. Where the hæmoglobin is diminished more than the count of corpuscles, we say that the color index is less than 1. For example, if a man has 5,000,000 red cells per cubic millimetre and only 50 per cent of hæmoglobin, we estimate the color index by simply reducing the count of cells to a stated percentage (5,000,000 cells = 100 per cent of cells) and dividing this percentage into the hæmoglobin percentage—*i.e.*, $\frac{50}{100} = 0.5$ = the color index. Therefore 4,000,000 red cells (= 80 per cent) with 60 per cent of hæmoglobin give a color index of $\frac{60}{80} = 0.75$.

The color index never goes above 1, except in pernicious anæmia (see below). As a rule when the red cells are above the normal the hæmoglobin rises equally, sometimes it lags behind a little, but rarely if ever does it rise higher than the cells.

In most anæmias, as has been pointed out, the hæmoglobin suffers markedly before any considerable loss of red cells takes place. In other words, the corpuscles get thin before they die, and except in malaria, hemorrhage, etc., and in a few other cases they are not destroyed while in the full vigor of health.

The loss of hæmoglobin is loss of albumin, the chief constituent of the cells, and hence is usually loss of weight.

In general the changes in the hæmoglobin are best studied in connection with changes in the count of red cells, and so far as they have not already been mentioned will come in under the various special diseases.

Fibrin.

The fibrin network to be seen in normal blood during coagulation (see page 41) is increased in a considerable number of conditions. Hayem has studied these minutely, and described several varieties of arrangement of fibrin fibres as characteristic of special diseases, that is, he studied fibrin qualitatively as well as quantitatively, and also as regards the rapidity of its formation.

The rate of fibrin formation is often not the same as the rate of coagulation. It is not parallel to the number of leucocytes or blood plates, at least not in all cases (malignant diseases, scurvy).

In a general way we expect increased fibrin in infectious and inflammatory diseases, but there are notable exceptions to this. The greater the exudation and the freer it is (in a cavity or on the surface) the thicker the fibrin network, while so-called interstitial inflammations or such conditions as parenchymatous nephritis show little increase in fibrin. The seat of the lesions has no considerable influence, except as it modifies the nature of the lesion. An abscess in one place has the same effect as an abscess elsewhere, provided it is equally free or equally confined, and of the same contents.

Tuberculosis does not increase fibrin if uncomplicated. Leucocytosis and fibrin behave alike in many respects, especially in relation to the vigor of resistance which the individual opposes to a given infection. When the individual is so weakened that he does not react well against the infection, the leucocytes and fibrin are but slightly increased, whereas in a vigorous individual the same infection would have markedly increased both fibrin and leucocytes. But neoplasms raise the count of leucocytes without changing the amount of fibrin.

In a general way fibrin increases and decreases as fever does, but often persists after fever is gone.

The most marked fibrin networks are seen in pneumonia, acute articular rheumatism, suppurative diseases, and in scurvy. In erysipelas it follows the leucocytes (increased in severe, not in mild cases). In the early days of grippe it is increased. The fever of hysteria or chlorosis shows no increase of fibrin

and post-hemorrhagic anæmia with or without fever shows none.

Fibrin is diminished in pernicious anæmia, not increased in leukæmia, typhoid, malaria, malignant disease, non-suppurative diseases of liver, nephritis (except interstitial nephritis, where it may be increased), heart disease, purpura, hæmoglobinuria (sometimes decreased).

The most valuable point about the fibrin appears to be the absence of any increase in malignant disease, whereby a diagnosis between the affection and a suppuration may be helped. Otherwise the information given by it is chiefly confirmatory of impressions given by other features in blood examination.

Lipæmia.

The blood invariably contains small quantities of fat, especially during digestion (v. Jaksch [1]).

In the blood of persons suffering from a variety of diseases such as phthisis, diabetes mellitus, obesity, alcoholism, nephritis, and in some dyspnœic conditions, as well as in health, fat is occasionally to be seen in considerable quantities. Grawitz [2] finds that if the blood is collected in a fine capillary tube and this is kept in a horizontal position for some time, fat rises to the surface like cream, and can be seen with an oil immersion lens in the form of fine drops. Gumprecht [3] demonstrated it with osmic acid, which stains the fat drops black, and proved them to be fat by dissolving them in ether, xylol, etc.

Lipæmia has no special significance so far as is known, and is not characteristic of the diseases above mentioned. Its cause is unknown.

[In almost any preparation of the fresh blood fat drops are to be seen unless the patient's skin is washed with alcohol before puncturing. Even with these precautions a few drops may often be seen in healthy people's blood.]

[1] "Klin. Diagnostik," p. 75 (English translation).
[2] *Loc. cit.*, p. 160.
[3] Deut. med. Woch., 1894, No. 39.

MELANÆMIA.

In malaria the occurrence of a black pigment in the leucocytes which have taken plasmodia into themselves, is generally to be seen during and shortly after a paroxysm. Pigment free in the blood is only to be seen at the moment of segmentation among the new generation of parasites. The same condition has been observed in relapsing fever and in persons suffering from melanotic malignant tumors, the pigment being always in the white corpuscles. Presumably it must at some time be free in the plasma, but it is rarely if ever seen outside the cells.

In Addison's disease Tschirkoff[1] observed pigment in the leucocytes.

HEMORRHAGE.

Women can stand a greater hemorrhage and yet live than men can. Children, on the other hand, succumb to comparatively slight hemorrhages (*cf.* Blood in Infancy, page 335). Individual differences make a great difference in the ability to survive hemorrhage, and no exact amount of blood can be stated as the maximum that any one can lose and yet survive.

Changes in the Blood Resulting from Hemorrhage.

The red cells and hæmoglobin of course suffer proportionally at first; later the hæmoglobin in the newly formed cells is always deficient (see below).

The striking point in the blood after hemorrhage is the evidence it gives us that even before the hemorrhage has ceased the other tissues begin to contribute fluid to make up the *volume* upon which life depends. The serum is markedly diluted by this fluid, but still serves to give the heart something to contract on and so prevents blood pressure from falling as fast as it otherwise would do. Were it not for such contributions from neighboring tissues the organism could sustain but slight hemorrhage without succumbing at once. We have then after hemorrhage a diluted or hydræmic blood, even though we do

[1] Zeit. f. klin. Med., vol. xix., 1891.

not assist the efforts of nature by contributing fluid by intravenous or rectal injection. Behier reports a case due to trauma in which the count was only 688,000 per cubic millimetre.

Coagulation increases in rapidity the more blood is lost, so that after severe hemorrhage it takes place almost instantly.

Blood Regeneration.

The regeneration of the blood after hemorrhage may be taken as typical of the same process in anæmia from other causes.

The length of time needed for full restoration to normal depends not merely on the (*a*) *amount* of blood lost, but also on the (*b*) age and nutrition of the patient as well as upon (*c*) the methods of *treatment* carried out and the existence of (*d*) other disease (typhoid, malignant disease, phthisis, etc.).

Allowing for these other conditions we may say that, other things being favorable, the loss of

I.	Less than	1	per cent of the blood mass is made up in	2 to 5 days.
II.	From	1 to 3	" " " " "	5 " 14 "
III.	"	3 " 4	" " " " "	14 " 30 "

The last amount means a very severe hemorrhage. Few surgical operations involve the loss of over three per cent, and after such accordingly we expect the blood to be normal again in two weeks, provided the individual is otherwise sound (see Malignant Disease, page 296).

Young, well-nourished persons are of course quicker in making up losses than the old and weak.

Blood Condition During Regeneration.

1. *Red Cells.*—(A) As previously mentioned, the hæmoglobin becomes relatively low as soon as the regenerative process is well established, and as recovery progresses the red cells are almost always normal in numbers for some time before the stature, weight, and color of the individual cells is what it should be. A color index of 0.50–0.60 is not unusual—in short, what some call a "chlorotic" condition of the blood.

(B) Qualitative changes are those already described on page 72, namely: (*a*) Deformities in size and shape with an average diminution in size; (*b*) polychromatophilic cells; and (*c*) nucle-

ated corpuscles. These latter are almost exclusively of the normoblast type, but an occasional megaloblast has been observed.

Blood Crises.—Von Noorden was the first to notice that in some cases nucleated corpuscles are to be found in the circulation in great numbers for a few hours only, the blood examination both before and after showing few or none at all. The name of "blood crisis" has been given to these sudden outpourings of nucleated red cells; they are to be observed during recovery from various forms of anæmia.

2. *White Cells.*—Immediately after a loss of blood we can usually find a decided *leucocytosis* despite the dilution of the blood (see above, Post-hemorrhagic Leucocytosis).

This leucocytosis is in no way different from those occurring from other causes. The percentage of adult cells is increased as usual, and the eosinophiles often disappear. The leucocytosis is rarely very high, seldom reaching over 30,000. It is not invariably present, or if present sometimes is of very short duration. Thus in a patient whose red cells were reduced to 3,200,000 by a profuse uterine hemorrhage the white cells counted next day were only 8,000; while in the next ward of the hospital was a man crushed in a railroad accident whose red cells were 1,280,000, and the white cells 28,000, the usual state of things.

The leucocytes may be increased even by a *cerebral hemorrhage* which is not large enough considerably to affect the red cells in most cases. Two apoplectic cases (with autopsy) observed at the Massachusetts Hospital showed:

1. Red cells 5,512,000, white cells 25,000, Hb. 85 per cent.
2. Red cells 5,560,000, white cells 15,600, Hb. 90 per cent.

Whether the leucocytes are here affected by any influence other than that of hemorrhage I do not know.

The effect of transfusion (intravenous saline solution) is apparently at first to increase the leucocytosis.

D——, a patient with traumatic rupture of the urethra, had had severe hemorrhage for forty-eight hours before it was checked at 1 P.M., November 1st, 1895. At 4 P.M., his pulse being 165, the count showed: red cells, 3,304,000; white cells, 10,400. He was at once given a pint of sterilized normal salt solution by intravenous injection under the strictest asepsis. Ten minutes after the transfusion the leucocytes numbered

32,400. One hour later they were 24,700, and the red cells 3,632,000. Four hours later leucocytes, 31,900; red cells, 3,046,000. The later counts were as follows:

		Red cells.	White cells.
November	2d: good pulse	3,608,000	34,600
"	2d (5 P.M.): good pulse	2,944,000	30,200
"	3d (4 P.M.): good pulse	2,928,000	15,800
"	13th	3,360,000	16,600

A good recovery was made.

Importance for Surgery of Blood Counting After Hemorrhage.

Mikulicz, who as a surgeon should speak with authority and who always takes account of the condition of the blood in his cases, lays down (following Laker) the following rule: *Never operate on any case when the hæmoglobin is below thirty per cent.* The question of operating at once or waiting for recovery from "shock," is a very common one in the accident rooms of any hospital and is generally settled on general impressions of the patient's vigor. We know, say, that he has lost blood, but we have no way of ascertaining how much. If his "shock" is due to hemorrhage he may need transfusion; if it is due to cerebral concussion or compression, the transfusion will do more harm than good. The blood count can settle these questions, and could reveal much which is now obscure, if it were more frequently employed in surgical cases and a standard like that of Mikulicz worked out.

In cases of suspected ruptured tube in extra-uterine pregnancy, the question of whether the patient is suffering from internal concealed hemorrhage can be settled in many cases by the blood count, which will show a decided loss of red cells if the hemorrhage is large, and thereby distinguish the condition from peritonitis, obstruction, or strangulated hernia, none of which affects the red cells. Any other concealed hemorrhage, as for instance from ruptured kidney or spleen or liver, may be indicated by the blood count when by other physical signs the diagnosis might be very difficult.

Summary.

The blood count is of importance after cases of supposed hemorrhage.

1. To ascertain whether such has taken place.
2. Its extent.
3. Whether operation is to be immediate or not.
4. Whether transfusion is indicated.
5. How soon the patient has got back enough blood to make operation worth while.

Chronic Hemorrhage.

Piles, uterine disease, hæmophilia, purpura, and other causes may produce a long-standing drain on the blood.

Some patients apparently can lose a little blood almost daily for years without acquiring any severe anæmia, and if the individual is otherwise sound and does not suffer from an underlying disease like phthisis, cancer, or nephritis, he can probably go on for a long time without showing any bad effects from the repeated small hemorrhages. *How* much he can stand we have no way of judging, for we cannot measure the amount of blood lost. When, however, such small repeated losses *do* produce an anæmia, regeneration is apt to be much slower than after a single large hemorrhage. The longer the drain has been going on the poorer the chance for recovery, and the slower the latter will be if it does take place.

Gain in body weight does not always mean gain in corpuscle substance as well (see Malignant Disease, page 290).

BOOK II.

SPECIAL PATHOLOGY OF THE BLOOD.

PART I.

DISEASES OF THE BLOOD.

CHAPTER I.

THE PRIMARY ANÆMIAS.

1. THE BLOOD IN PERNICIOUS ANÆMIA

THE definition of the disease has been sufficiently explained before (see page 70) and we can proceed at once to the description of the blood.

1. Gross appearances.

(*a*) The drop as it emerges from the puncture is often excessively pale and watery, but not more so than may occasionally be seen in secondary anæmia or chlorosis. Sometimes it is not nearly so pale as in other cases with equally low counts, a fact which may be due to the increased color index sometimes present (see below). In one case (color index 1.2) I have seen the blood as red as normal.

Another appearance, which I have frequently observed in this and other anæmias, is an uneven, streaked color in the drop, as if the cells were unequally divided in the plasma.

(*b*) As striking as the color of the drop is its great fluidity; the rapidity with which it slips off the ear or finger often makes it difficult to suck it up in time. It is usually very slow in coagulating.

2. The fresh specimen in most cases shows no rouleaux formation, a diminution in blood plates and fibrin, and usually great variations in the size and shape of the corpuscles. Not infrequently the deformed corpuscle shows active pseudo-amœboid motions of its projecting points or of the cell as a whole. The great lack both of red and white cells is noticeable even in the slide and cover-glass specimen.

Red Cells and Hæmoglobin.

(*a*) Quantitative changes (see Table I.). The average count of red cells in the fifty-two cases of my table is about 1,200,000, which may be taken as the average count in patients seen at the stage of the disease at which they feel sick enough to seek medical advice. We very rarely get an opportunity to examine the blood in the early stages of the disease, so that we have to judge of them chiefly from the evidence given during the remission so commonly observed. In the relapse following such a remission the blood count may fall from 5,000,000 to 1,000,000 in a period of from six weeks to six months. In the later stages of the disease 500,000 red cells per cubic millimetre is not rare, and if the diminution has been gradual, the patient may be up and about and able to do light work with a count no greater than this. I had an opportunity to observe such a case in the wards of Dr. F. C. Shattuck at the Massachusetts General Hospital five years ago, where for several weeks the blood count remained at or near 500,000, yet the patient was outdoors daily, read the papers, and seemed perfectly comfortable.

The lowest count on record is that reported by Quincke—143,000 per cubic millimetre.

TABLE I.

No.	(*a*) First Count.		(*b*) Highest Count.		(*c*) Lowest Count.		Total number of examinations.
	Red cells.	Per cent hæmoglobin.	Red cells.	Per cent hæmoglobin.	Red cells.	Per cent hæmoglobin.	
1	490,000	?	490,000	?	410,000	?	2
2	510,000	20	680,000	?	510,000	20	3
3	600,000	24	....	....	....	....	1
4	630,000	?	658,000	?	45,000	?	13
5	670,000	?	670,000	....	670,000	....	1
6	680,000	20	680,000	20	680,000	20	1
7	735,000	?	1,500,000	?	730,000	?	3
8	784,000	14	784,000	14	784,000	14	1
9	842,000	?	842,000	?	842,000	?	1
10	896,000	18	896,000	18	430,000	6	3
11	896,000	17	3,800,000	70	608,000	15	20
12	962,000	15	1,028,080	15	962,000	15	3
13	988,000	?	....	....	....	....	1
14	992,593	34	1,080,000	?	992,593	34	2
15	1,096,400	12	1,096,400	13	624,000	13	4
16	1,060,524	35	....	....	....	....	1
17	1,111,000	?	1,111,000	?	756,000	?	3

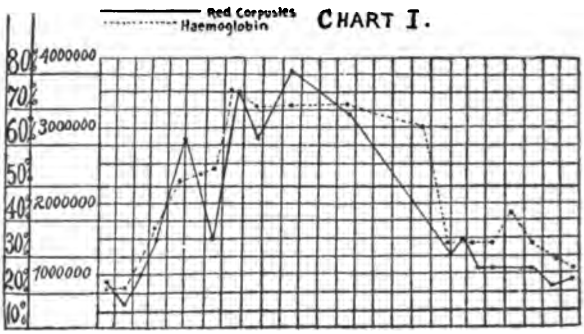
TABLE I.—(*Continued*).

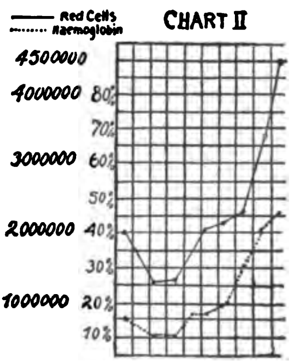
No.	(a) First Count. Red cells.	Per cent hæmoglobin.	(b) Highest Count. Red cells.	Per cent hæmoglobin.	(c) Lowest Count. Red cells.	Per cent hæmoglobin.	Total number of examinations.
18	1,118,000	18	2,820,000	?	1,038,000	?	8
19	1,126,000	?	1,126,000	?	1,100,000	?	2
20	1,137,000	20	1,137,000	20	550,000	15	4
21	1,140,000	20	1,140,000	20	622,160	25	3
22	1,150,000	?	2,802,000	....	1,150,000	....	16
23	1,150,000	30	....	....	....	....	1
24	1,176,000	29	....	....	....	....	1
25	1,200,000	15	....	....	....	....	1
26	1,226,284	25	4,450,000	65	762,000	?	12
27	1,270,000	16	2,700,000	30	....	....	2
28	1,288,000	?	1,910,000	?	1,288,000	....	3
29	1,289,000	32	1,628,000	34	1,121,000	34	5
30	1,300,000	28	1,300,000	28	970,000	30	2
31	1,336,000	28	1,336,000	28	956,000	20	3
32	1,344,000	23	1,344,000	23	758,000	17	3
33	1,493,000	32	1,500,000	?	....	....	2
34	1,498,000	20–30	....	....	....	....	1
35	1,500,000	35	3,700,000	53	1,460,000	30	8
36	1,582,000	20	4,760,000	52	1,624,000	30	12
37	1,588,000	20	1,768,000	40	1,500,000	20	4
38	1,600,000	25	4,032,000	80	1,288,000	23	10
39	1,627,000	?	....	....	....	....	1
40	1,755,000	20	1,755,000	20	1,117,000	20	2
41	1,768,000	?	2,458,000	?	1,768,000	?	6
42	1,800,000	28	2,868,000	41	1,508,000	31	5
43	1,800,000	25	....	....	....	....	1
44	1,800,000	30	1,800,000	30	1,768,000	22	3
45	1,819,000	34					
46	1,872,000	25	1,872,000	25	1,144,000	30	3
47	1,884,000	....	1,889,314	....	1,330,000	....	4
48	1,984,000	39	1,984,000	39	598,000	15	3
49	2,000,000	20	2,000,000	20	1,200,000	20	2
50	2,080,000	35	5,056,000	70	1,632,000	50 (?)	9
51	2,076,000	15	4,500,000	45	1,384,000	10	10
52	2,524,000	26	2,524,000	26	1,280,000	13	5
	Average= 1,200,000	26					220
							Average = 4+

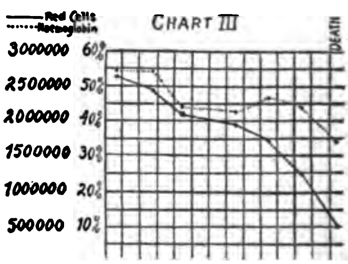
The great but temporary improvements above alluded to, followed by relapse, occur either with or without treatment. In the course of a few months the count of red cells may rise to normal, the nucleated corpuscles (see below) disappear, and the patient is apparently restored to health. I have followed one case through five such relapses in a period of three years before the fatal issue came. Frequently the patient feels so well

during one of these remissions that he goes to work and is lost sight of, and, under such conditions, the incautious are apt to report "cure."

The *accompanying charts*[1] show the three types usually met







with; No. II. being, of course, only a fragment of No. I., while the steady progression of No. III. may have been preceded by a rise from a former downfall, though no such history was obtained.

Looking over a considerable number of cases, one can hardly help being struck with the tendency of the count to remain near the figure 1,000,000. Cases rarely remain stationary at, say, 2,000,000, and often die without sinking below 1,000,000. It seems as if some self-applying mechanism

[1] The number of perpendicular lines represents the number of weeks.

tended to arrest the destruction of corpuscles at or near this point (see Table I.).

TABLE II.—WHITE CELLS—FIRST EXAMINATION.

No.	White Cells.	No.	White Cells.	No.	White Cells.
1	400	17	3,200	33	5,600
2	500	18	3,200	34	6,000
3	800	19	3,500	35	6,000
4	1,000	20	3,600	36	6,000
5	1,000	21	3,704	37	6,400
6	1,000	22	4,000	38	6,500
7	1,500	23	4,000	39	7,000
8	1,600	24	4,000	40	7,200
9	1,800	25	4,000	41	7,500
10	2,000	26	4,200	42	7,600
11	2,000	27	4,500	43	9,000
12	2,000	28	4,720	44	9,600
13	2,000	29	4,828	45	10,000
14	2,800	30	4,900	46	10,100
15	2,800	31	5,200		
16	3,000	32	5,300	Average = 4,200+	

In counting the red cells some difficulty and error may result from the very small size of some of the cells. It is especially important that the diluting solution should be clean and freshly made, else without the aid of a stain it may be hard to distinguish the dwarf cells or microcytes from bits of extraneous substance.

Quantitative Changes.

White corpuscles (see Table II.).—The rule is a very considerable diminution in the number of leucocytes. Thus of forty-six cases which I have examined thirty were under 5,000, the average of all being 4,200+.

[I have excluded from this series counts made immediately after hemorrhages and counts in infants. The latter are very apt to show a leucocytosis in connection with *any* form of anæmia.]

As the disease progresses the leucocytes fall even more rapidly than the red cells and counts as low as 500 white cells per cubic millimetre are not uncommon.

Leucocytosis when present in the blood of adult cases is always due to some complication like hemorrhage or suppuration.

As mentioned above, the blood plates and fibrin are much diminished.

In four cases in which Dr. Lindström, of Boston, was kind enough to give massage, we were unable to see the slightest gain either in corpuscles or hæmoglobin, such as can be produced temporarily in most healthy persons. The observations of J. Mitchell on this point we were unable to confirm.

Hæmoglobin.

A certain number of cases of pernicious anæmia have a relatively high percentage of hæmoglobin (*e.g.*, 1,000,000 red cells and 35 per cent of hæmoglobin, or a color index of 1.75). In many cases this is not so, and in others we cannot tell whether it is so or not, owing to the unreliability of the v. Fleischl instrument when used for very low hæmoglobin percentages.

Of the 34 cases in the series on page 118, in which the hæmoglobin was tested, a color index of over 1 was apparently present in 13, or 38 per cent, and a color index of less than 1 in 21 or 62 per cent, of the cases. How many of these hæmoglobin estimations may have been wrong I cannot say.

From the frequency with which we find the corpuscles larger than normal in pernicious anæmia (see below), we should expect that the hæmoglobin *would* be relatively high, and in a larger percentage of cases than the v. Fleischl instrument indicated.

An increased color index is probably a bad prognostic sign. In the remissions of the disease when the cells are increasing fast, the hæmoglobin lags behind and the color index is *low*. As the relapse follows, the color index in many cases progressively increases. Cases *whose color index is low* and in which the average diameter of the red cells is normal *are apt to be gaining at that time*, while those with high color index are apt to be losing at that time.

The average color index in the 39 cases in which the hæmoglobin and red cells were both tested was 1.04, the average percentage of hæmoglobin being 26 and of corpuscles 24 (= 1,200,000).

Qualitative Changes.

1. *Red Corpuscles.*

(*a*) *Increase in the average diameter* of the cells is a very constant and striking feature of the stained specimens in this disease. In no other disease do so large cells or so many of them occur.

Out of twenty-eight cases in which I have looked for this point, twenty-one showed the increase, as far as could be judged without actually measuring any large number of cells. This does not mean that every cell is larger than normal, but that those larger than normal outnumber those undersized; the "macrocytes" are more numerous than the "microcytes." Occasionally we see cells over 20 μ in diameter, some with nuclei, some without.

(*b*) *Deformities in Shape.*—The eye soon gets used to the shapes assumed by the necrobiotic corpuscles and learns to distinguish them from the distortions due to technique or to crenation. Most of them fall under one or another of the types shown in Plate IV. Litten has laid particular stress on the horseshoe forms, and thinks them peculiar to pernicious anæmia. The battledore and sausage-shaped forms are very common. In one case I found all the red cells of the latter shape, so that they looked at first sight like a lot of gigantic bacilli. That this appearance was not due to the technique (as I had at first supposed) is probable from the fact that the rod-shaped cells did not point all in one direction as they would have done if pulled out of shape by the process of spreading.

Occasionally we see cases with no considerable deformities whatever in the red cells. In nine cases out of thirty in which this point was observed, little or no deformity was noted. I cannot make out that such cases have any better or worse prognosis than others. I have never seen cases whose red cells were all *undersized*, but a normal average diameter was present in somewhat over one-quarter of the cases in which I have looked out for this point.

[1] Some writers advise the use of less heat than usual in dealing with cover-glass specimens of pernicious anæmia. I have not found this so and heat as usual for fifteen minutes at 100° C.

(c) *Staining Properties of the Red Cells.*—The white spots or streaks described by Maragliano, Hayem, and others are very often seen in the red cells of pernicious anæmia despite good technique. Some corpuscles are so pale in the centre that we see only the narrow ring of stained protoplasm at the periphery, a mere shell. Others are swollen up so as to show no sign of central biconcavity, and stain deeply and evenly all over.

More common than in any other form of anæmia are the polychromatophilic red corpuscles (see Plate IV.) which with the Ehrlich-Biondi mixture stain brownish, purple, or gray, either as a whole or in parts. In the nucleated red cells the protoplasm is very apt to show this change, so that it is often difficult to distinguish them from lymphocytes. In difficult cases we have sometimes to fall back upon the appearances of the edge or periphery, which in most red corpuscles shows some thin place or crinkle characteristic of a *flat* cell, while the lymphocyte gives us the more solid-looking outline of the *spherical* cell.

All these microchemical changes can be better brought out with hæmatoxylon-eosin or eosin-methyl-blue stains, but all that is needed for clinical purposes can be made out with the ordinary Ehrlich-Biondi mixture.

Nucleated Red Corpuscles.

Nothing further needs to be said in description of these forms (see above, pages 75–80). We have no *exact* method of estimating the number of nucleated cells either in relation to the whole number of red cells or in a cubic millimetre. All we can do is to note the number seen in *such* an area of a cover-glass specimen as is covered while counting a given number of white cells, say 1,000. Knowing the ratio of red to white corpuscles, we can calculate from this number of nucleated red cells their approximate relation to the whole number of red cells.

Thus if the ratio of white to red be 1:1000 (1,000,000 red and 1,000 white) and we have seen two nucleated red corpuscles while making a differential count of 1,000 white cells, the total number of red cells passed over must be approximately 1,000,000 and the number of nucleated corpuscles about two in 1,000,000 red cells or two in a cubic millimetre. Of course where leucocytosis is present and the ratio is raised—say to 1:150

(10,000 white and 1,500,000 red)—finding two nucleated red cells while counting 1,000 white would mean that there were two nucleated cells in every 150,000 non-nucleated, or twenty in a cubic millimetre (or in 1,500,000 non-nucleated cells).

Such calculations are inaccurate because we are never sure that the red cells and white cells are distributed in the dried specimen exactly as they are in the blood. Part of the leucocytes may be accumulated at the edges of the cover-glass so that the ratio in the middle may be different from that in the circulating blood.

Nevertheless we can get some idea of how plentiful the nucleated corpuscles are, and as their significance in prognosis depends far more on their *kind* than on their *number*, greater accuracy as to the latter is not at present important. For instances, two megaloblasts per cubic millimetre mean a worse prognosis than twenty normoblasts, provided there are no other kinds present in either case. It is the *ratio* of megaloblasts to normoblasts and not the absolute number of each, that is of importance.

In all of the thirty-eight cases of pernicious anæmia in which I have examined the blood, the number of megaloblasts has exceeded the number of normoblasts, and as the cases grew worse the megaloblasts grew relatively more numerous (often absolutely as well).

The range of variation in the number of nucleated cells present has extended in my series from six per cubic millimetre to 7,100 per cubic millimetre (see Table III.). The calculation can be made by using the following formula.

Let n = the number of white cells counted (by differential count).
" m = " " nucleated red cells seen while counting these.
" p = " " white cells per cubic millimetre (Thoma-Zeiss).

$p \times \frac{m}{n} = x =$ number of nucleated red cells per cubic millimetre.

The search for nucleated corpuscles in pernicious anæmia is sometimes the most laborious undertaking in all blood examination, but it is also one of the most important. We may search two or three hours before finding one nucleated corpuscle, but on that corpuscle may hang the character of our prognosis. If it be a megaloblast and no other nucleated red corpuscles are seen, the prognosis is bad, and it is impor-

tant that we should know it. This is particularly true when the case is seen during a remission, for under these conditions we might never suspect a case of pernicious anæmia but for the presence of megaloblasts. They are not always difficult to find; indeed, in one of my cases they were nearly as numerous as the white cells, but, as a rule, we do not get off with less than two hours' work.

The following table (Table III.) shows the number of nucleated corpuscles per cubic millimetre in thirty of the cases examined by the writer.

TABLE III.—NUMBER OF NUCLEATED RED CELLS PER CUBIC MILLIMETRE IN THIRTY CASES OF PERNICIOUS ANÆMIA.

Case Number.	Total nucleated red cells.	Megaloblasts.	Normoblasts.	Microblasts.
1	7,100	5,300	1,325	475
2	6,468	3,476	924	2,068
3	854	574	266	14
4	277	277	0	0
5	240	160	80	
6	229	123	106	
7	208	130	78	
8	200	134	66	
9	117	103	14	
10	116	80	36	
11	114	95	19	
12	112	96	16	
13	96	96	0	
14	96	84	12	
15	92	59	33	
16	46	26	20	
17	45	36	9	
18	39	33	6	
19	35	32	3	
20	28	26	2	
21	28	21	7	
22	28	28	0	
23	18	12	6	
24	14	14	0	
25	11	11	0	
26	11	10	1	
27	11	9	2	
28	9	6	3	
29	8	7	1	
30	3	2	1	

White Corpuscles.

Qualitative Changes.—Unless the cover-glasses are spread unusually thick, it may take a long time to find enough leu-

cocytes for an accurate differential count, so great is the leucopenia in many cases. It is worth while, therefore, to spread some cover-glasses more thickly than would be advisable if we had only the red cells to examine. Such preparations should be dried at once by artificial heat.

Lymphocytosis is the chief feature (see Table IV.).

TABLE IV.—PERCENTAGES OF LEUCOCYTES IN PERNICIOUS ANÆMIA.

Lymphocytes.		Eosinophiles.		Number of count.
No.	Per cent.	No.	Per cent.	
1	79.	1	9.	1
2	71.	2	6.2	1
3	61.6	3	4.7	2
4	57.6	4	4.6	2
5	57.2	5	4.5	3
6	53.8	6	4.4	1
7	51.5	7	4.3	1
8	49.5	8	4.	5
9	47.9	9	4.	1
10	47.9	10	3.7	2
11	45.9	11	3.5	1
12	44.7	12	3.4	1
13	43.7	13	3.1	1
14	42.2	14	2.8	2
15	41.	15	2.7	2
16	40.8	16	2.6	1
17	40.5	17	2.	1
18	38.	18	1.5	5
19	38.	19	1.5	2
20	37.8	20	1.5	1
21	35.7	21	1.5	1
22	35.6	22	1.4	1
23	35.6	23	1.2	1
24	34.	24	1.2	1
25	33.1	25	.8	1
26	33.	26	.8	1
27	29.4	27	.8	1
28	27.2	28	.6	1
29	26.5	29	.5	1
30	24.2	30	?	1
31	22.	31	0	1
32	21.2	32	.0	1
33	19.8	33	.0	1
34	16.	34	.0	

In 34 cases examined by myself the lymphocytes (large and small) averaged 45.9 per cent. About nine-tenths of these were small forms. As the fatal termination approaches, the percentage of lymphocytes rises. An extreme case of this change has

already been recorded on page 90. Two other cases showed respectively 71 and 79 per cent of lymphocytes a few days before death. The adult cells suffer proportionately.

Eosinophiles are occasionally increased, 9 per cent being present in one of my cases, 6.6 per cent in another. The average of 49 examinations in my 34 cases is 2.7 per cent.

Small percentages of *myelocytes* are the rule. They are present in 29 of my 35 cases. The following table shows the percentages:

TABLE V.

No.	Percentage of myelocytes.	No.	Percentage of myelocytes.	No.	Percentage of myelocytes.
1	9.2	13........	2.0	25.......	0.6
2	8.8	14........	1.8	26........	.6
3	8.	15........	1.5	27........	.5
4	6.	16........	1.2	28........	.4
5	4.6	17........	1.	29........	.3
6	4.	18........	1.	30........	.2
7	3.6	19........	1.	31........	.0
8	3.4	20........	1.	32........	.0
9	2.7	21........	.8	33........	.0
10	2.5	22........	.8	34........	.0
11	2.2	23........	.6	35........	.0
12	2.2	24........	.6	Average=2 per cent.	

As has been explained above (page 105), the myelocyte is found in a great variety of affections, although very sparingly in most, but, so far as my observations go, its presence is more constant and the percentages run higher in pernicious anæmia than in any other disease except leukæmia. I am speaking now of percentages. With a leucopenia such as is usually present in pernicious anæmia, 2 per cent of myelocytes means absolutely a very small number per cubic millimetre.

Taking 4,200 leucocytes per cubic millimetre as the average for pernicious anæmia (see above page 121) 2 per cent of myelocytes amounts to only 84 per cubic millimetre. In leukæmia the absolute number of myelocytes is seldom under 50,000 per cubic millimetre.

The more important characteristics of the blood of pernicious anæmia are as follows:

1. *Red cells about 1,000,000 per cubic millimetre.*
2. *White cells much diminished.*

3. Hæmoglobin variable, *sometimes increased* relatively (= high-color index).
4. Deformities in size and shape of red cells in many cases.
5. *Increase in average diameter of red cells.*
6. Polychromatophilic red cells.
7. *Megaloblasts more numerous than normobalsts.*
8. Lymphocytosis.
9. Small percentage of myelocytes.

The items italicized are the most important and characteristic.

Diagnostic Value.

1. *Pernicious anæmia and chlorosis* may be indistinguishable without the examination of the blood. The pallor of the two diseases is not always different either in degree or in kind, and the symptoms and physical signs may be identical.

The differential diagnosis is easily made by the blood. The red cells rarely reach as low as 2,000,000 in chlorosis and the number and degree of degenerative changes are less than in pernicious anæmia. Megaloblasts have been seen in chlorosis (Hammerschlag) but have never constituted a majority of the nucleated red cells present. In the great majority of cases the pallor and other signs and symptoms of chlorosis are due to lack of hæmoglobin per corpuscle (for the corpuscles are not only pale but very small-sized), and not to a lack of corpuscles. The high-color index and large size of the scanty cells in pernicious anæmia constrast strongly with this.

The white cells are about the same in both diseases, though usually fewer in pernicious anæmia.. Lymphocytosis is common to both diseases. Myelocytes are occasionally found in chlorosis, but much less commonly than in pernicious anæmia.

2. *Pernicious Anæmia and the Anæmia of Malignant Disease.*—Not long ago I examined the blood of a gentleman who had gradually and without assignable cause acquired a "lemon-yellow" pallor, without loss of flesh, vomiting, pain, or any localizing sign or symptom. The diagnosis of pernicious anæmia had been made. To my great surprise I found over 4,000,000 red cells, with only thirty-eight per cent of hæmoglobin, and 18,780 white cells, eighty-six per cent of which were of the adult type. One normoblast was seen. Fibrin was not increased. The

anæmia was evidently secondary, and the autopsy ten months later showed cancer of the stomach.

Malignant disease may bring down the count of red cells to 1,000,000 or lower, but *in such cases* leucocytosis is always present. As will be seen in the chapter on malignant disease, leucocytosis is by no means invariable in the anæmia of cancerous growth, but *in those cases* which cause such an anæmia as to resemble the counts of pernicious anæmia, leucocytosis is invariable. This in itself is sufficient to exclude uncomplicated pernicious anæmia. Where an actual increase in the whole number of leucocytes is not present in malignant disease, there is often an increased percentage of adult cells, contrasting strongly with the increased percentage of young cells in pernicious anæmia. Normoblasts and not megaloblasts are the rule in malignant disease. If megaloblasts are present they are in the minority, while in pernicious anæmia they are in the majority.

3. *Pernicious Anæmia and other Secondary Anæmias.*—Almost all secondary anæmias which are severe enough to reduce the count of red cells below 2,000,000 follow the type of malignant disease and show leucocytosis. The great pallor and dyspnœa seen in connection with some cases of *tuberculosis* and *nephritis* rarely mean a low count of red cells, but simply a loss of hæmoglobin. I remember two cases in adjacent beds at the Massachusetts General Hospital, both with extreme yellow pallor without emaciation; one had 1,020,000 and the other 4,100,000 red cells, the hæmoglobin in each being about thirty per cent. The first was pernicious anæmia, the second nephritis.

Purpura, typhoid, lead poisoning, chronic malaria, and other diseases may reduce the red cells to a point as low as that seen in early stages of pernicious anæmia and may *not be accompanied by leucocytosis;* but the absence of changes most characteristic of the latter disease (a majority of megaloblasts, increased diameter and color index in the red cells) serves to make the diagnosis clear.[1]

4. *Pernicious Anæmia and Leukæmia.*—Occasionally in in-

[1] Another point of difference emphasized by Grawitz is that the plasma of pernicious anæmia has a relatively larger amount of solids than that of anæmia secondary to the above diseases. This is hardly a clinically applicable test, but is said to be a valuable one.

fants these two diseases seem to approach very near each other and are difficult to distinguish. In infancy, as is well known, any anæmia (primary or secondary) is apt to be accompanied by leucocytosis and an enlarged spleen. Further leukæmia, which in adults usually causes a relatively slight anæmia, affects the red cells much more strongly in infancy, and may reduce them to a number decidedly suggestive of pernicious anæmia. Therefore in both diseases we may have enlarged spleen, great anæmia, and leucocytosis.

The one characteristic point of leukæmic blood—the abundance of myelocytes—usually enables us to distinguish the two diseases, for although present in both diseases the myelocyte is much more plentiful in leukæmia. Unfortunately we have no way of fixing just *how* numerous myelocytes must be in order to constitute leukæmia. It is only in infancy and very rarely then that this difficulty arises, but at that period I am inclined to believe that we sometimes see conditions intermediate between the two diseases, indicating the ultimate identity of the two. Their numerous clinical resemblances cannot here be discussed. (For further comment on this point see page 345.)

Prognostic Value of the Blood in Pernicious Anæmia.

The prognosis is always very bad, but the following scheme indicates the presence of a severe or of a mild type:

1. *Severe (rapidly fatal).*	2. *Less Severe (slower course).*
(*a*) Extreme progressive anæmia.	(*a*) Remissions.
(*b*) High-color index.	(*b*) Normal or low-color index.
(*c*) Increase in size of red cells.	(*c*) Normal-sized cells.
(*d*) Degenerative changes.	(*d*) No degenerative change.
(*e*) Numerous megaloblasts.	(*e*) Numerous normoblasts.
(*f*) Few or no normoblasts.	(*f*) Few megaloblasts.
(*g*) Lymphocytosis.	(*g*) Normal percentage of adult cells.

It has been thought by some observers that the absence or great scantiness of nucleated corpuscles indicated lack of any effort at regeneration on the part of the blood-making functions and hence a peculiarly malignant type of the disease. I have never seen cases in which no nucleated corpuscles were present,

but their scantiness has seemed to me as a rule to be associated with a more *slowly* fatal type of the disease.

No significance has seemed to me to attach to the presence of larger or smaller percentages of eosinophiles.

	Pernicious anæmia.	Chlorosis.	Secondary anæmia.	Leukæmia in infancy.
Red cells	About 1,000,000	Rarely under 2,000,000.	May be 1,000,000 or less.	May be under 2,000,000.
White cells....	Usually decreased.	Usually normal....	Usually increased.	Usually more increased than in any other disease.
Hæmoglobin ..	Often relatively high.	Always relatively low.	Relatively low...	Relatively low.
Megaloblasts ..	Constitute the majority of the nucleated red cells.	Rare.	Rare; never more numerous than normoblasts.	Common.
Normoblasts ..	Less numerous than the megaloblasts.	Occasional; always more numerous than megaloblasts.	Common	Common.
Size of red cells	Increased.........	Diminished..	Various; not increased.	Various; not increased.
Lymphocytes..	Increased.........	Increased	Usually diminished.	Usually increased.
Adult leucocytes.	Decreased	Decreased.........	Usually increased.	Usually diminished.
Myelocytes....	Common.....	Rare...............	Rare	Usually more numerous than in other diseases.

2. THE BLOOD IN CHLOROSIS.

This has been already described for the most part under the heading of Secondary Anæmia. In many cases the two are indistinguishable by the blood examination alone, the changes consisting simply in the presence of light, small-sized, pale, more or less deformed red cells whose number may or may not be decreased, according to the severity of the case. Leucocytosis is rarely if ever present in uncomplicated chlorosis, but is often absent in secondary anæmia. Normoblasts may be present in both. The chief points of distinction are:

(*a*) The red cells are more apt to be uniformly undersized and under-colored in chlorosis, while in secondary anæmia we more often find normal cells among the diseased ones.

(*b*) The color index may be lower in chlorosis than is common in secondary anæmia, and this lowering is more constant in chlorosis.

(*c*) Lymphocytosis, which is very common in chlorosis, is not so common in secondary anæmia.

(*d*) Nucleated corpuscles are less common in chlorosis than in anæmia secondary to malignant disease.

(*e*) Coagulation is rapid, in contrast with the very slow clotting of pernicious anæmia and of many secondary anæmias. Yet fibrin is not increased.

The Blood in Gross.

The pallor of the drop is sometimes excessive, fully as great as in pernicious anæmia, and the liquid is very fluid and thin. Yet it coagulates very rapidly and our technique must be prompt.

RED CELLS AND HÆMOGLOBIN.

Quantitative Changes.

Hayem has recorded cases whose count was as low as 1,662,000 and even 937,360 per cubic millimetre. Such figures are certainly rare in this country, and the striking fact is usually the *slight* numerical loss of red cells, considering the extreme pallor of the patients.

The lowest count in the Massachusetts Hospital series was 1,932,000, and in W. S. Thayer's sixty-three cases 1,953,000. The accompanying Table VI., from the Massachusetts Hospital records, shows the range of red cells and hæmoglobin in seventy-seven cases as counted when the patients first came under observation. The highest counts (7,100,000 and 5,884,000) are undoubtedly due to some temporary stasis or concentration of the blood.

The average of the 77 cases, 4,050,000 red cells per cubic millimetre, is remarkable in so nearly coinciding with Thayer's[1] series above referred to, the average of which is 4,096,544.

The average hæmoglobin percentage of this series, 41.2 per cent, is also very close to Thayer's (42.3 per cent). This gives us on the average a reduction of the corpuscle substance to one-half the normal, or to the equivalent of 2,250,000 healthy red cells; 49 of the 77 cases have 4,000,000 or more red cells. These figures do not agree with those collected by v. Limbeck, in which only 99 out of 247 are over 4,000,000. But this prob-

[1] See Osler's article on Chlorosis in the "American Text-Book of Medicine," vol. ii., 1894.

ably means simply that in this country the patients seek medical advice before their disease has advanced very far, while in Germany they wait longer before resorting to a hospital. For, as above explained, in all anæmias the individual corpuscles lose substance first and only after some time begin to decline in number. This is especially the case in chlorosis, although by no means peculiar to that disease.

The color index is invariably low, as seen in the table, although it is rare to see it fall below .30. In only four cases of the present series did it go below that figure, the average being about .50.

TABLE VI.—CHLOROSIS.

No.	Red cells.	Per cent Hæmoglobin.	Color index.
1	7,100,000	50	.35
2	5,884,000	68	.58
3	5,620,000	58	.51
4	5,512,000	51	.46
5	5,488,000	45	.41
6	5,480,000	50	.46
7	5,456,000	60	.55
8	5,448,000	58	.53
9	5,416,000	50	.46
10	5,180,300	35	.34
11	5,176,000	37	.36
12	5,136,000	50	.49
13	5,096,000	58	.56
14	5,080,000	50	.50
15	5,040,000	78	.78
16	5,030,000	58	.58
17	5,000,000	35	.35
18	4,992,000	82	.82
19	4,968,000	40	.40
20	4,960,000	55	.56
21	4,910,000	50	.51
22	4,904,000	65	.61
23	4,904,000	40	.40
24	4,888,000	38	.38
25	4,712,000	51	.54
26	4,712,000	56	.59
27	4,711,000	42	.42
28	4,680,000	48	.52
29	4,640,000	60	.64
30	4,600,000	50	.54
31	4,560,000	45	.50
32	4,520,000	32	.35
33	4,448,000	45	.50
34	4,416,000	40	.45
35	4,380,000	54	.62
36	4,312,000	35	.40
37	4,250,000	67	.80

TABLE VI.—CHLOROSIS (*Continued*).

No.	Red cells.	Per cent. Hæmoglobin.	Color index.
38	4,216,000	35	.41
39	4,208,000	32	.38
40	4,170,000	57	.70
41	4,160,000	25	.30
42	4,128,000	..	..
43	4,104,000	28	.34
44	4,096,000	30	.36
45	4,080,000	21	(!).26
46	4,072,000	52	.63
47	4,024,000	40	.50
48	4,016,000	44	.55
49	4,000,000	30	.37
50	3,986,000	61	.76
51	3,985,000	42	.52
52	3,944,000	30	.36
53	3,920,000	47	.60
54	3,888,000	37	.50
55	3,800,000	32	.42
56	3,800,000	40	.52
57	3,688,000	53	.70
58	3,688,000	48	.64
59	3,680,000	55	.73
60	3,648,000	37	.50
61	3,648,000	37	.50
62	3,620,000	20	(!).27
63	3,512,000	30	.42
64	3,512,500	26	.37
65	3,504,000	40	.56
66	3,460,000	..	..
67	3,320,000	34	.50
68	3,244,000	..	..
69	3,200,000	19	(!).29
70	2,992,000	34	.56
71	2,992,000	31	.51
72	2,936,000	26	.44
73	2,584,000	14	(!).28
74	2,552,000	19	.38
75	2,472,000	15	.31
76	2,464,000	18	.37
77	1,932,000	19	.50
Average	4,050,000+	41	.50

The striking contrast is with pernicious anæmia, rather than with secondary anæmia. In the former the color index, as above mentioned, averaged 1.04 in 39 cases. In secondary anæmia it is almost always below 1, but does not *average* so low as in chlorosis, although in individual cases it may be very low.

For example, Osterspey quotes a case of gastric cancer with

a blood count of 4,230,000 red cells, and only 22 per cent of hæmoglobin, a color index of .26.

Red Cells (Continued).

Qualitative Changes.

(*a*) The stained specimen shows a greater or less degree of *pallor of the corpuscle centres* corresponding so accurately to the diminution in hæmoglobin that a practised observer can tell approximately how low it is simply from the stained specimen. The pallor, however, is to be taken in connection with the *size* of the cells, for the diminution in hæmoglobin is not due simply to a bleaching out of the cells, but to their loss of size. Hence,

(*b*) The *diminution in the average diameter* of the cells is a very important feature. Both in this respect and as regards the bleaching of individual cells, many cases contrast with most secondary anæmias, in that a large proportion of the cells are affected alike, *i.e*, are small and pale, while in secondary anæmia there are apt to be well-stained and good-sized or oversized cells in every field. These last occur also in chlorosis, but less frequently as a rule. Hence the usually lower color index of chlorosis. In certain cases this distinction does not hold and the two conditions are identical in so far as the size and color of the red cells are concerned. It is to the white cells that we must look for help in differential diagnosis.

(*c*) *Deformities in size and shape* are very common in all advanced cases, but often absent in mild or moderate ones. They present no special peculiarities except that macrocytes are relatively rare and microcytes relatively common. In the severest cases, however, the macrocytes begin to get more numerous and we approach the picture of pernicious anæmia.

(*d*) *Degenerative changes* (Maragliano) are not common but are occasionally present in severe cases.

(*e*) *Nucleated red corpuscles* are *very* scanty even in advanced cases. Hayem never saw any, but most observers find them in small numbers after long search. They are almost always of the normoblast type, but megaloblasts have also been found.

The scantiness of nucleated red cells is a point of contrast with the anæmia secondary to malignant disease, in which even in mildly anæmic states we readily find nucleated corpuscles, while

in chlorosis, even in severe cases, a long search may show very few or even none at all.

Specific Gravity.

Chlorosis is usually agreed to be one of the diseases in which specific gravity and hæmoglobin run parallel, and as the inaccuracies and inconveniences of the v. Fleischl instrument are so great, it seems to the writer better to follow the specific gravity rather than the hæmoglobin. The tables on page 31 (Part I.) show how the inference from density to coloring matter can be made. A specific gravity of 1030 is not very rare.

White Cells.

A. Quantitative Changes.

Leucocytosis is absent in uncomplicated cases. In the series in Table VII. the occasional leucocytosis may be due to digestive or to a variety of other influences (uterine troubles, etc.), which could not be excluded.

TABLE VII.—Leucocytes in Chlorosis.

No.	White corpuscles.	No.	White corpuscles.	No.	White corpuscles
1.......	15,000	27......	8,000	53......	6,100
2.......	14,400	28......	7,949	54......	6,000
3.......	12,800	29......	7,900	55......	6,000
4.......	12,000	30......	7,600	56......	6,000
5.......	12,000	31......	7,600	57......	5,600
6.......	12,000	32......	7,600	58......	5,600
7.......	11,600	33......	7,600	59......	5,600
8.......	11,200	34......	7,600	60......	5,200
9.......	11,100	35......	7,440	61......	5,200
10.......	10,800	36......	7,200	62......	5,200
11.......	10,800	37......	7,200	63.	5,000
12.......	10,500	38......	7,200	64......	4,800
13.......	10,400	39......	7,000	65......	4,800
14.......	10,000	40......	7,000	66......	4,172
15.......	10,000	41......	7,000	67......	4,000
16.......	10,000	42......	7,000	68......	4,000
17.......	10,000	43......	7,000	69......	4,000
18.......	10,000	44......	7,000	70......	4,000
19.......	9,600	45......	6,850	71......	3,600
20.......	9,600	46......	6,800	72......	3,600
21.......	9,600	47......	6,800	73......	3,400
22.......	8,500	48......	6,600	74......	3,200
23.......	8,000	49......	6,600	75......	2,800
24.......	8,000	50......	6,400	76......	1,500
25.......	8,000	51......	6,400		
26.......	8,000	52......	6,200	Average = 7,485	

The average in Thayer's sixty-three cases was 8,467; in the present series (see Table VII.) it is 7,485.

As in pernicious anæmia, the worst cases are apt to have leucopenia, and as improvement progresses the white rise even faster than the red corpuscles.

The absence of leucocytosis is the most important point in distinguishing chlorosis from secondary anæmia due to cancer, suppuration, etc.

B. Qualitative Changes.

Lymphocytosis is usually present, as in pernicious anæmia, wherever the disease is well marked, and sometimes even in mild cases. Thus Rieder found in 12 cases an average of 33 per cent of young cells, the highest percentages being 53.7, 43.5, and 41.7. Either the small or the large lymphocytes may predominate. In my own experience it has usually been the small forms.

The adult cells suffer proportionally, their low percentage contrasting often with that of secondary anæmia associated with leucocytosis. Eosinophiles are occasionally increased. In Rieder's 12 cases the average percentage was 3.5, the highest percentages being 9.6 and 7 per cent.

Myelocytes are rare but have occasionally been observed in small numbers.

Regeneration of the Blood.

As the patients begin to mend under the influence of treatment, the blood changes are just the reverse of those seen during the development of the disease. First the corpuscles gain in numbers, the hæmoglobin still remaining low; later and much more slowly the coloring matter, size, and weight of the cells are renewed. It seems as if the new-formed cells were of light weight and had to grow up, or be replaced gradually by cells of normal stature. The nucleated corpuscles and deformities disappear and the leucocytes shoot up often a little above the normal.

Blood Plates.

Usually considerably increased.

Summary.

1. Blood as a whole: Very pale in marked cases, very fluid, but coagulates rapidly. Fibrin not increased. Specific gravity usually low, running parallel with the hæmoglobin.

2. Red cells: Average 4,000,000 when patient is first seen, very rarely go below 1,000,000. The majority of them are *small-sized, pale,* often deformed. Nucleated corpuscles are rare (normoblasts as a rule).

3. White cells, not increased.

Lymphocytosis, occasionally eosinophilia.

4. Blood plates increased.

Diagnostic Value.

1. The points of difference from pernicious anæmia have been discussed.

2. It is important to distinguish it from simple debility, and from cases whose skin only is anæmic; in both of these conditions the blood is normal.

3. From secondary anæmia it may be indistinguishable in case the latter be without leucocytosis. Where leucocytosis is constantly present and the percentage of adult leucocytes is increased, chlorosis (uncomplicated) can be excluded. Of course many of the complications which may occur in chlorosis are accompanied by leucocytosis.

CHAPTER II.

LEUKÆMIA AND HODGKIN'S DISEASE.

THE distinction between leukæmia and leucocytosis has been sufficiently dwelt on above.

The vast majority of cases fall clearly under one or the other of two distinct types, the splenic-myelogenous on the one hand, and the lymphatic on the other. Pure splenic and pure myelogenous cases are so rare that they may practically be disregarded. The lymphatic forms usually show some enlargement of the spleen (as well as the marked glandular swellings), but nothing like the enormous hypertrophy of the splenic-myelogenous type. On the other hand, the lymph glands may be slightly enlarged in cases of the splenic-myelogenous type, but much less than in the lymphatic form.

Corresponding to these two clinical types we have two very different blood conditions. Mixed forms occur where some characteristics of each type are present, both clinically and in the blood examination, but these are rare.

Either form may be acute or chronic, although the lymphatic form is much more apt to be acute and the splenic-myelogenous type to pursue a slower course. Thus of the five cases of lymphatic leukæmia seen by the writer three were acute, one subacute (six months), and one chronic (over three years), while of twenty splenic-myelogenous cases all were chronic.

1. SPLENIC-MYELOGENOUS FORM.

The drop as it emerges from the puncture looks perfectly natural in color and is neither whitish nor chocolate colored. It flows very sluggishly, however, and is difficult to spread between cover-glasses owing to the masses of white cells contained in it. Coagulation is slow.

RED CELLS.

The diminution in red cells is moderate, averaging about 3,120,000 in the thirty-four cases of Table VIII., A (here the five lymphatic cases are included). The patients are often not pale and may feel perfectly well. The hæmoglobin is usually diminished, the color index apparently remaining about normal. It is difficult to read the v. Fleischl instrument in leukæmia as the presence of so many leucocytes gives a muddy tint to the liquid, not easy to compare with the red of the glass.

TABLE VIII.—LEUKÆMIA.

A.		B.	
No.	Red cells, count.	No.	White cells, count.
1	5,000,000	1	1,072,222
2	4,877,000	2	980,000
3	4,800,000	3	820,000
4	4,288,000	4	800,000
5	4,016,000	5	756,000
6	3,760,000	6	748,000
7	3,635,570	7	656,000
8	3,605,000	8	626,600
9	3,292,000	9	570,000
10	3,200,000	10	500,000
11	3,078,000	11	492,000
12	3,010,000	12	454,000
13	2,996,000	13	430,000
14	2,938,000	14	428,000
15	2,921,600	15	400,000
16	2,868,000	16	394,000
17	2,792,000	17	386,000
18	2,738,000	18	340,000
19	2,715,000	19	320,000
20	2,576,000	20	290,000
21	2,520,000	21	260,000
22	2,322,222	22	220,500
23	2,320,000	23	213,000
24	2,256,000	24	188,000
25	2,140,000	25	183,000
26	2,112,000	26	170,000
27	2,060,000	27	139,600
28	2,016,000	28	138,000
29	1,866,664	29	134,400
30	1,420,000	30	132,000
31	1,386,000	31	98,000
32	1,358,000		
33	1,200,000		Average = 438,000
34	408,000		
	Average = 3,120,000+		

Qualitative Changes.

The striking point is the presence of very numerous nucleated red cells even in the absence of *any sign of anæmia.* With over 4,000,000 well-formed and well-colored red cells, we may have hundreds of nucleated ones in every cover-glass. They are as numerous in this form of leukæmia as in the worst forms of pernicious anæmia, even though the patient may be feeling nearly well.

Both normoblasts and megaloblasts may be seen, but in most cases the latter are much in the minority. Many of the normoblasts show fragmentation in their nuclei and occasionally true karyokinetic figures are to be seen. In the anæmic cases we find all the other changes in the red cells characteristic of anæmia, but the nucleated cells are always more prominent than in any other form of anæmia of a like severity. This shows that nucleated corpuscles are not to be thought of as evidence (like deformities in shape) of regenerative or degenerative conditions only. A special connection to the bone marrow is very clearly indicated, all the more so as in the lymphatic form of the disease in which the bone marrow is not affected, nucleated corpuscles are much less numerous, appearing in small numbers even in the very anæmic cases and not at all in those who are not anæmic.

Other qualitative changes are not marked and correspond to the degree of anæmia present; often there are none at all.

As the count of the white cells rises, that of the red may fall and *vice versa;* or the red cells may remain at a comparatively high figure despite the progress of the white.

White Cells.

Quantitative Changes.

The average number per cubic millimetre in the thirty cases of Table VIII., B (the lymphatic cases being excluded) was 438,000 at the time when the cases first came under observation. The highest count in this series is 1,072,222 and the lowest 98,000.

Cases are on record in which the white cells were actually more numerous than the red. The average ratio in my series is

about one white to seven red. The highest ratio is 1:2, and the lowest 1:37. It is best to use the "red counter" with a dilution of 1:200 in counting the white cells, otherwise they are often too crowded for convenience. The hæmatokrit is useful in this disease and in any condition where the white cells are much increased, not to supersede the Thoma-Zeiss or to give us the absolute number of cells, but for comparative observations as to the length of the column of white cells from day to day in a given case.

In the fresh specimen we notice that a large proportion of the white cells are not amœboid, a point of marked contrast with leucocytosis, in which nearly all the leucocytes are amœboid. This is due to the fact that the myelocytes which form so large a portion of the leucocytes in this disease do not possess the faculty of amœboid motion. We should expect therefore to find their nucleus free from the twists and distortions characteristic of the amœboid (polymorphonuclear) cells. And this is in fact the case (see below).

With or without the influence of therapeutic agencies the white cells may fall gradually to normal and remain there for some time, the patient feeling greatly improved. Such a case occurred under my observation, and the patient, a washerwoman, went back to work and afterward passed through an attack of lobar pneumonia in safety.

At such a time, when no increase in the white cells is present, we should never suspect leukæmia, seeing the case for the first time, unless we chance to make a differential count; then the characteristic qualitative changes (see below) would be seen.

TABLE IX.—LEUKÆMIA (SPLENIC-MYELOGENOUS).

Case.	Percentage of myelocytes.	Percentage of eosinophiles.	Case.	Percentage of myelocytes.	Percentage of eosinophiles.
1........	60.	11.	11........	32.	3.
2........	55.	8.	12.......	31.	3.
3........	51.	6.5	13........	30.3	3.
4	50.	6.1	14........	26.	2.7
5........	48.	6.	15........	26.	2.5
6........	46.	5.	16........	26.	2.5
7........	42.	5.	17........	21.4	1.8
8........	38.	4.	18........	20.4	1.5
9........	36.	4.			
10........	33.	4.	Average =	37.7	4.4

Qualitative Changes.

The enormous number of myelocytes is the point of interest. The average percentage in my 18 cases was 37.7 per cent (see Table IX), rising in one case as high as 60 per cent and never lower than 20 per cent.

Taking the average total number of leucocytes as 438,000 per cubic millimetre, the absolute number of myelocytes would be over 162,000 per cubic millimetre. So far as I am aware the highest count of myelocytes in any other disease is that mentioned on page 128 in a case of pernicious anæmia, namely, 1,150 per cubic millimetre. The contrast is sufficiently striking. I wish to insist upon this point, namely, that the blood of splenic-myelogenous leukæmia is absolutely peculiar and characteristic, and could not be confused with that of any other disease. Certain writers of late years have concluded that because myelocytes do occur in a great variety of diseases as well as in leukæmia, therefore there is nothing peculiar about the blood of the latter affection. It would be as logical to say that because albumin and casts occur occasionally in the urine of persons practically well, therefore there is nothing characteristic about the urine of acute nephritis.

Between the largest number of myelocytes ever recorded in any disease other than leukæmia, and the smallest number ever found in the latter disease, there is as great a difference as there is between the minute traces of sugar to be found in normal urine and the marked glycosuria of diabetes mellitus.

At the first glance the stained specimen of leukæmic blood seems to be composed mostly of myelocytes, but this is because they are on the average so much larger than the other forms of white cells, which, being packed away in the interstices between the large myelocytes, do not appear prominently at first sight.

Although (as just mentioned) the average size of the myelocytes is greater than that of any other kind of leucocyte, there is a great range of variation in their size, and some are hardly, if at all, larger than a red cell. (This is equally true of the myelocytes as seen in the bone marrow. See above, page 57.)

The individual characteristics and variations in the myelocytes have been already sufficiently described on page 55.

PLATE II.

FIG. 1.—Both this and Fig. 2 are intended to be fac-similes of actual microscopic fields.

(*a*) Note the cell between those labelled 8 and 9—apparently a polymorphonuclear cell without neutrophilic granules. Such cells are often seen in this form of leukæmia.

(*b*) Note also the cell at the extreme upper right-hand corner of Fig. 1, which it is almost impossible to classify either as a myelocyte or as a polymorphonuclear neutrophile, since it *appears* to be intermediate between the two varieties.

(*c*) Both the nucleated corpuscles are normoblast; 9 has polychromatophilic protoplasm. The red cells show scarcely any deformities and very slight deficiency in coloring matter.

FIG. 2.—(*a*) Note the deformities in size and shape of red corpuscles, owing to the anæmia present.

(*b*) No lymphocytes are figured, as they made up only two per cent of the white cells in this case. Eosinophiles were absent.

(*c*) Note that the contrast between this figure (leucocytosis) and the one above it (leukæmia) is not in the abundance of white cells but in the *kind* of white cell predominating among those present.

Examination of the Blood.

PLATE II.

Figure I = Splenic-myelogenous Leucaemia
Figure II = Leucocytosis (cancer of kidney)
Cells stained yellow = Red corpuscles
1. 2. 3. 4 a. 5 = Polymorphonuclear neutrophiles
6 = Lymphocyte
7 a. 8 = Eosinophiles
9 a. 10 = Nucleated red corpuscles
All others = Myelocytes

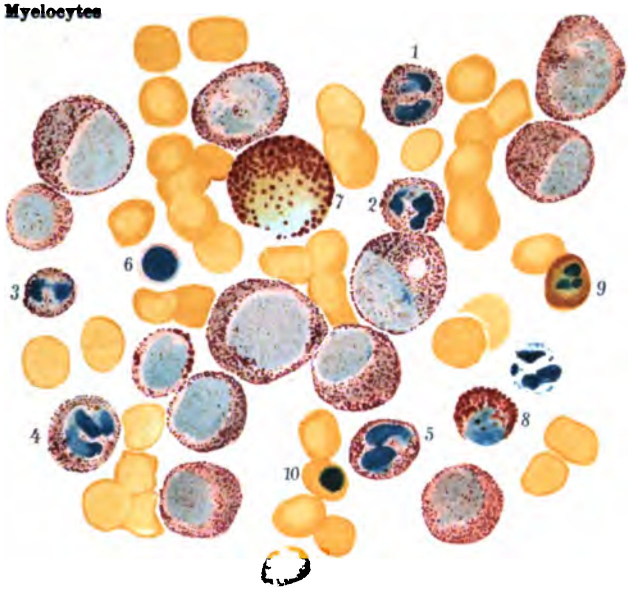


Figure I
Leucaemia.

0 10 20
Scale of μ

Cells stained yellow = Red corpuscles
All others = Polymorpho-nuclear-neutrophiles

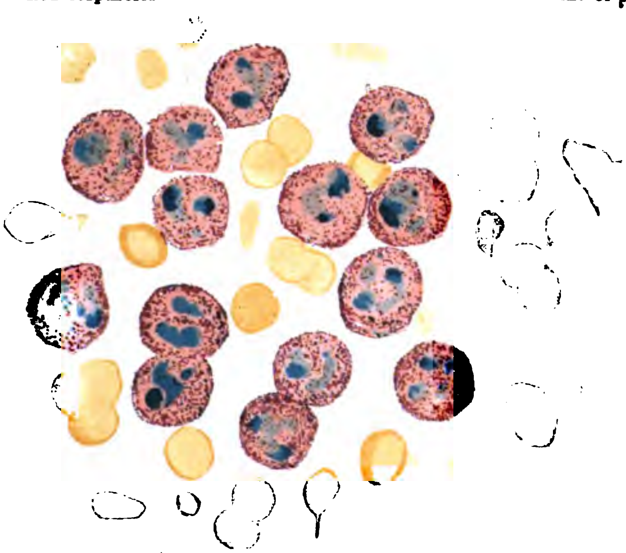


Figure II
Leucocytosis.

R. C. Cabot fec.

Lith. Anst. v. E. A. Funke, Leipzig.

Polymorphonuclear Cells.

Although absolutely the number of these cells is greatly increased, the number in each 1,000 leucocytes is considerably diminished. The average percentage in the eighteen cases of Table X. is 49.2 per cent, the figures ranging between twenty-six and sixty-six per cent.

Table X.—Leukæmia (Splenic-Myelogenous).

No.	Percentage of polymorphonuclear cells.	Percentage of lymphocytes.	No.	Percentage of polymorphonuclear cells.	Percentage of lymphocytes.
1........	26.	2.	12........	51.	6.
2........	32.	2.	13........	54.	8.
3........	37.	2.5	14........	55.	8.
4........	40.	2.5	15........	61.	9.
5........	44.	2.5	16........	62.3	9.
6........	45.	2.6	17........	62.5	18.9
7........	46.	3.	18........	66.	31.
8........	46.	5.			
9........	49.5	5.	Average =	49.2	7.6
10........	50.	5.			
11........	50.6	6.			

The individual cells show a much greater range of variation in size, staining properties, and the size and shape of the nucleus than in any other condition. In most forms of leucocytosis, for example, one adult cell looks very much like another, but in this form of leukæmia we are often struck by—

(*a*) *Very small* cells.

(*b*) *Dark stained* or very *pale stained* cells.

(*c*) Unusual shapes in the nuclei.

Besides these variations we often see cells apparently belonging to this type, but whose protoplasm shows no color whatever. Such a cell is figured to the right of Plate II., Fig. 1. Other cells show a few granules scattered about against a perfectly white background. The outer rim of the cell is usually stained faintly, so that we can hardly make out its outline.

(*d*) There are always some cells on the border line between the polymorphonuclear and the myelocyte, and in regard to which decision must be arbitrary. We cannot help getting the impression that at any rate in *this* disease the two varieties are only different stages in the development of the same cell.

Lymphocytes.

It is here that the greater relative *diminution* occurs, to make room for the incursion of the myelocytes. In percentages they are reduced from their normal, 20 to 30 per cent, to an average of 7.6 per cent, as in leucocytosis. But still their absolute number is always increased. Thus the lowest percentage present in Table X. (namely, two per cent) would mean 8,760 out of the average 438,000, the total leucocyte count per cubic millimetre, and 8,760 is three or four times as many lymphocytes per cubic millimetre as are present in normal blood.

The proportion of large and small forms among the lymphocytes varies a great deal, but there is no such excess of the large forms as would be expected if the spleen were the source of these cells, as Ehrlich supposed.

There is nothing peculiar about the lymphocytes which differ in no respect from those of normal blood.

Eosinophiles.

Like all the other varieties these are *absolutely* much increased. Relatively—by percentages—they may or may not be so. In my series they ranged from 1.5 to 11 per cent, averaging 4.4 per cent, a slight increase over the normal.

Many writers, wrongly interpreting Ehrlich's observations on this point, have stated that an increased percentage of eosinophilic cells was the distinguishing mark of leukæmia, and even recent writers (*e.g.*, Gilbert, Strümpell) continue to repeat this false statement.

The cell characteristic of splenic-myelogenous leukæmia is not the eosinophile but the myelocyte.

We distinguish several types of eosinophiles in leukæmic blood.

(*a*) Ordinary (polymorphonuclear) eosinophiles.
(*b*) Eosinophilic dwarf cells.
(*c*) Eosinophilic myelocytes.

(*a*) Needs no comment; (*b*) is simply a very small cell with eosinophilic granules; sometimes such cells are not over 5 μ in diameter. They are not uncommon in this form of leukæmia and are very rare in any other disease. The same is true of (*c*), the eosinophilic myelocytes which are very rare in any

other disease, except pernicious anæmia, where they are occasionally seen.

These cells are like myelocytes except that their granules are eosinophilic instead of neutrophilic (see Plate I. and Plate II.). They are found in the marrow in considerable numbers and constitute the majority of the eosinophilic cells seen in this form of leukæmia. Other constituents of leukæmic blood are (occasionally) basophilic cells, white cells showing mitosis (especially the myelocytes), and the so-called Charcot-Leyden crystals. (As these last have no diagnostic value and are not peculiar to any disease, no description of them will be given here. They appear to be present wherever eosinophiles are plentiful, *e.g.*, in asthma, gonorrhœa, in the bone marrow, etc.).

Neusser's perinuclear basophilic granules are said to be abundant in this disease, owing to the excess of uric acid in the system.

During remissions, when the leucocyte count may fall to normal, the percentage of myelocytes remains large and the diagnosis could usually be made even if we saw the case then for the first time. This I have observed in two cases, and Thayer has had the same experience.

LYMPHATIC LEUKÆMIA.

Although Fraenkel has maintained that all cases of lymphatic leukæmia are acute and that therefore the difference between the two forms of the disease rests simply on the rapidity of the process in the blood and clinically, there is no doubt that chronic lymphatic leukæmia exists.

Fraenkel is enabled to maintain his position only by extending the term *acute* to cover all cases whose symptoms last not more than four months. Six weeks is the limit agreed upon by most other observers.

The writer has watched two cases of typical lymphatic leukæmia for periods of seven months and two years respectively. The latter was as little sick as any case of leukæmia that I have ever seen and came over thirty miles from time to time to report at the Out-Patient department. His blood showed little variation from the following figures: Red cells, 2,300,886; white cells, 112,000.

The differential count always showed the overwhelming majority (over ninety per cent) of small lymphocytes characteristic of the disease. The lymph glands were all much enlarged, the spleen just palpable. The patient kept about his work as a gardener for over two years. Grawitz has watched a similar case for over four years.

Red Cells.

The count of red cells is often somewhat lower than in the splenic-myelogenous form of the disease, averaging 2,730,000 in my cases.

The point of interest is the *comparative rarity of nucleated red cells*, the abundance of which is so marked a feature of splenic-myelogenous leukæmia. They follow the grade of anæmia present. Cases occurring in children show more abundant nucleated corpuscles (the same is true of all leukæmia in children) than those occurring in adults, and the megaloblasts, usually scanty, may equal the number of normoblasts.

White Cells.

Quantitative Changes.

The numerical increase is not nearly so marked as in the splenic-myelogenous form. The average ratio of white to red cells is about 1:40 instead of 1:7, and we never see counts reach the height common in the other form of the disease. The highest count of my series was 220,000 and the lowest 30,000, the average being 141,000 as compared with 438,000 in the other form.

Qualitative Changes.

Lymphocytes (small forms, large forms, or a mixture) make up usually over ninety per cent of all the leucocytes present. In some cases they are all nearly of one size, while in others we find every gradation from the smallest to the largest, so that it is absolutely futile to attempt to separate them into "large" and "small." Two of my cases were made up wholly of the small forms all under 11 μ in diameter, two were composed largely of forms over 15 μ in diameter, while one showed every intermediate size.

PLATE III.

(*a*) *Lymphatic Leukæmia* with Excess of Small Lymphocytes.

One polymorphonuclear cell is present. All the rest are lymphocytes and exemplify the variations in the morphology of the cell occuring in this and other diseases as well as in health, *e.g.*, variations in the staining of the protoplasm and nucleus, indentation and even division of the nucleus.

Note that the scale of the whole of Plate III. is larger than in the other plates (see scale of μ).

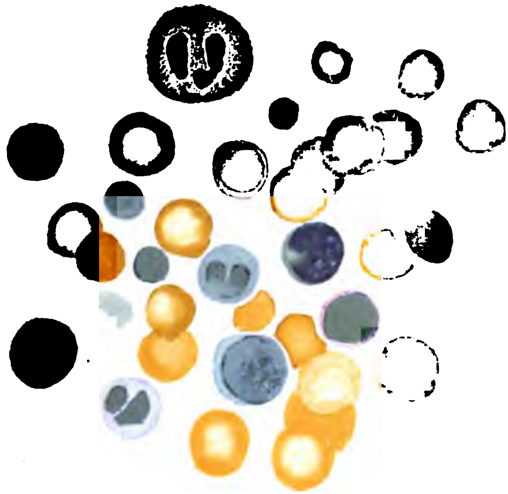
(*b*) *Lymphatic Leukæmia* with Excess of Large Lymphocytes.

The symptoms, signs, and course of these two cases were closely similar, both subacute (eight weeks).

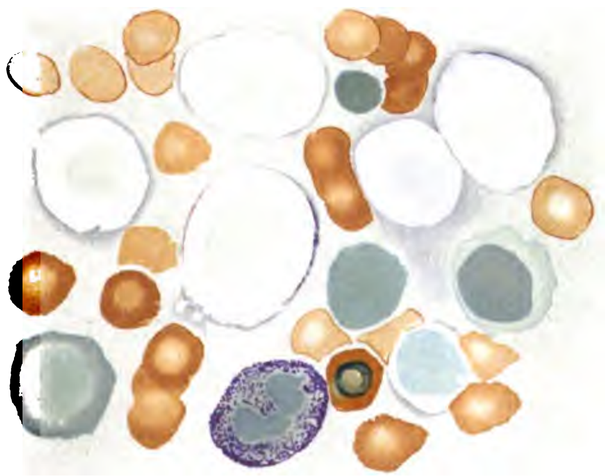
Note the lack of chromatin in both nuclei and protoplasm of large lymphocytes. The plasma around them or their extreme edge took most of the stain. The brown tint of the red cells is due to underheating.

PLATE III.

a



b



Lymphatic Leucaemia

a. Small Lymphocytes in excess
b. Large „ „ „

0 10 20
Scale of μ

R. C. Cabot fec.

Lith. Anst v. E. A. Funke, Leipzig.

TABLE XI.—LYMPHATIC LEUKÆMIA.

Case.	Percentage of lymphocytes.	Percentage of polymorphonuclear cells.	Percentage of myelocytes.	Percentage of eosinophiles.
1	98.6	0.5	0.8	0.0
2	98.6	1.	.37	.1
3	96.5	3.4	.0	.1
4	94.	5.7	.37	.0
5	91.8	4.6	2.	1.6
Average = 95.9		3.04	0.7	0.36

Sometimes, especially where the large cells predominate, the staining is very faint throughout the nucleus and protoplasm (see Plate III., *b*), so that at first sight we should think something was wrong with our technique. Other forms of leucocytes in the same preparation, however, will stain normally, showing that the trouble is in the lymphocytes and not in the technique.

The protoplasm may be entirely unstained as in most of the cells in Plate III., *b*, or it may stain pale gray or pink. In other specimens, especially those of the small-cell type (Plate, III., *a*) the lymphocytes stain well. Their nuclei are frequently indented or even divided in two (this occurs also in normal blood, but less often).

In acute cases Litten has noticed fatty degeneration in the leucocytes (11th Cong. f. inner. Med., 1893).

The following figures illustrate the influence of a septicæmia (from suppurating cervical glands) which ended the life of No. 3 in the above Table XI.

Date.	Number of leucocytes.	Percentage of lymphocytes.
April 3d	31,600	96.5
" 4th	31,000	
" 6th	28,505	93.6
" 8th	44,000	
" 10th	31,500	95.5
" 12th	40,000	
" 13th	Sepsis began.	
" 20th	5,661	
" 21st	4,000	
" 22d	3,400	92.
" 24th	3,222	
" 28th	800	
" 29th	471	94.7
Death on the 29th.		

Zeissl's case, also of the lymphatic form, showed the following:

Date.	White cells.	Percentage of lymphocytes.	Percentage of adult cells.
September 9th	80,000	96.	4.
" 24th	113,000		
" 26th	119,000		
" 29th	122,000	97.8	2.
October 6th	140,000		
" 9th	Pneumonia began.	99.	1
" 10th	119,000		
" 11th	98,000		
" 12th	68,500		
" 13th	43,500	88.7	11.3
" 14th	50,000		
" 15th	9,350	85.4	14.6
" 16th (A.M.)	133,200		
" 16th (P.M.)	172,000	75.	25.

Summary.

The leading characteristics of leukæmic blood are as follows.

(*a*) *Splenic-myelogenous Form.*

1. Red cells about 3,000,000, nucleated forms very numerous.
2. White cells about 450,000, of which
3. Myelocytes form about thirty per cent.

(*b*) *Lymphatic Form.*

1. Red cells about 3,000,000 or lower; nucleated forms rare.
2. White cells about 100,000 or lower, of which
3. Lymphocytes form over ninety per cent (the large or the small forms may predominate).
4. Myelocytes and eosinophiles very scanty.

(*c*) *Mixed forms* occasionally occur, partaking of the characteristics of each of the above.

Diagnostic Value.

Leukæmia is distinguished by the blood examination from

1. Hodgkin's disease: (*a*) splenic, (*b*) glandular.
2. Tumors of the spleen and vicinity (*e.g.*, kidney or retroperitoneal glands).
3. Enlargements of the lymphatic glands from tuberculosis, syphilis, malignant disease.
4. Hydronephrosis.
5. Huge leucocytosis from any cause.

6. Chronic malaria.
7. Amyloid disease.

1. *Leukæmia and Hodgkin's disease* (lymphadenoma or pseudo-leukæmia). The pathology of the two diseases is identical but for the blood count. In Hodgkin's disease the blood is normal, or shows at most a moderate anæmia or leucocytosis (adult cells alone increased), and the diagnosis is easily made.

2. *Tumors of the spleen* and more especially of the *kidney* are very apt to be mistaken for leukæmia. Within a single year I have been asked to examine the blood in three cases of "leukæmia," all of which turned out to be malignant disease of the kidney. In all of these there was a large tumor resembling the spleen in the left hypochondrium and a very large increase of white cells. In two of them the blood was examined fresh and the great number of white cells in the slide taken as evidence confirmatory of leukæmia. The stained specimen, however, showed only marked leucocytosis with ninety per cent of adult cells of the ordinary type and no myelocytes. Other large tumors of this region showed similar results.

3. *Adenitis* with hyperplasia due to tuberculosis shows usually normal blood[1] and is thus easily distinguished from leukæmia. Leucocytosis is often present in syphilitic cases and still more marked in those due to cancer or sarcoma, but the counts rarely reach 30,000 and myelocytes are absent or very scanty.

4. One case of *hydronephrosis* in which the distention of the sac was so great that it presented as a hard, solid tumor on the right hypochondrium, was taken for leukæmia by a competent observer some years ago. The *normal* blood examination revealed the mistake, and excluded also malignant disease in all probability. The diagnosis was only reached, however, at the autopsy.

5. Huge leucocytosis in pneumonia or malignant disease may often cross the old boundary line of 100,000 white cells, beyond which none but leukæmic cases were supposed to venture. The differential count sets us right instantly, showing ninety per cent or so of the increase to be made up of ordinary adult leucocytes.

6 and 7. The large spleen and cachectic appearance associated

[1] Sometimes marked leucopenia.

with chronic malaria and long-standing suppurations may be easily distinguished from leukæmia by the absence of anything more than anæmia and leucocytosis in the blood.

	Red cells.	White cells.	Young leucocytes.	Adult leucocytes.	Myelocytes.	Nucleated red cells.
Leukæmia (splenic-myelogenous).	About 3,000,000	450,000 ±	About 7.6 per cent.	About 50 per cent.	About 37 per cent.	Very numerous.
Leukæmia (lymphatic).	About 3,000,000	100,000 ±	About 96 per cent.	About 3 per cent.	Absent.	Rare.
Hodgkin's disease..	About normal.	7,500 ±	Normal.	Normal.	Absent.	Absent.
Tumors of or near the spleen.	Usually diminished.	20,000 to 40,000 ±	Greatly decreased.	Greatly increased,	Few if any.	Few.
Leucocytosis in general.	....	May be over 100,000	Greatly decreased.	Greatly increased.	Few if any.	Few at times.
Chronic malaria....	Much diminished.	Somewhat increased.	Usually increased.	Usually decreased.	Few if any.	Few.
Amyloid disease....	Usually diminished.	Usually increased.	Usually decreased.	Usually increased.	Absent.	May be a few.
Hydronephrosis....	Normal.	Normal.	Normal or decreased.	Normal.	Absent.	Absent.

EFFECT OF INTERCURRENT INFECTIONS.

There are on record seventeen cases in which leukæmia (acute or chronic) has been complicated with some intercurrent infection, with marked effect upon the blood in all but one. This single case was an acute rheumatic arthritis reported by Richter in the discussion of Fraenkel's article in the *Deutsche medicinische Wochenschrift* for 1895 (Nos. 39, 43, and 45), p. 639. Here the blood remained unchanged.

Müller's[1] case of lymphatic leukæmia was complicated by a septicæmia and the count of white cells *rose* from 180,000 to 400,000 per cubic millimetre, with a marked increase in the percentage of polymorphonuclear cells. Here was a genuine leucocytosis added to a leukæmia.

With the exception of these two cases, all those hitherto published have shown a marked progressive *decrease* in the total number of leucocytes without any change in the percentages of the different varieties in twelve, while the other five showed like Müller's an increased percentage of the polymorphonuclear cells despite the decrease in the total leucocyte count.

Various infections—miliary tuberculosis, pneumonia, grippe, erysipelas, abscess of kidney, septic lymph glands—alike de-

[1] Müller: Deut. Archiv für klin. Med., 1892, vol. 50, p. 47.

creased the leucocyte count. In one case a rise just before death was observed.[1]

Thus in Henck's case the leucocytes fell from 400,500 to 89,000, in one of Müller's from 246,900 to 57,300, in Kovács' from 67,000 to 17,000, in Zeissl's from 140,000 to 9,350. I have already mentioned a case of lymphatic leukæmia (page 149) in which the leucocytes fell from 40,000 to under 500, this last being on the day of death. In this case the percentages of the different varieties of leucocytes remained entirely unchanged.

It appears, therefore, that when an infection complicates leukæmia we may have—

1. No effect (see case of rheumatic fever as a complication, just mentioned).
2. A genuine leucocytosis on top, so to speak, of the leukæmia, with an increased percentage of polymorphonuclear cells.
3. A decrease in the leucocyte count with or without an increase of polymorphonuclear cells. This decrease is by far the most common result and may go far below normal as death approaches.

Goldschneider[2] found that by the injection of splenic extract and other substances he could bring about a similar diminution in the number of leucocytes, but that, as in the case of intercurrent infections, this diminution was not accompanied by any improvement in the patient's condition and death followed as usual.

[1] 1. Eisenlohr: Virchow's Archiv, vol. 73, ... 1 case.
2. Henck: Virchow's Archiv, vol. 78, ... 1 "
3. Quincke: Ref. in Münch. med. Woch., No. 1, 1890, . 1 "
4. Stintzig: *Ibidem*, ... 1 "
5. Ortner: Wien. klin. Woch., 1890, p. 832, . . . 1 "
6. Müller: Deut. Archiv f. klin. Med., 1891, vol. 48, and 1892, vol. 50, ... 2 cases.
7. Kovács: Wien. klin. Woch., 1893, p. 701 . . . 1 case.
8. Fraenkel: Deut. med. Woch., 1895, p. 639, . . . 2 cases.
9. Heubner: *Ibidem* (in discussing Fraenkel's cases) 1 case.
10. Richter: *Ibidem* (in discussing Fraenkel's cases) 3 cases.
11. Freudenstein: Ref. by Fraenkel, *loc. cit.*, . . . 1 case.
12. Zeissl: Wien. klin. Woch., May 14th, 1896, . . . 1 "
13. Personal observation, ... 1 "

Total, ... 17 cases.

[2] Discussion of Fraenkel's article, *loc. cit.*

Abscesses occurring in leukæmic patients are filled with adult leucocytes as ordinary abscesses are, and do not contain myelocytes.

HODGKIN'S DISEASE.

(*Pseudo-Leukæmia, Lymphoma*).

The diagnosis of this disease is impossible without the blood count. Its pathology is identical with that of leukæmia and even post mortem the two diseases are indistinguishable so far as the lesions outside of the blood are concerned. Yet the blood is in no way peculiar, but presents in most cases all the characteristics of the normal tissue. Its value is as negative evidence, telling us in a given case that leukæmia is absent even though all the other signs and symptoms may be those of leukæmia.

(I.) Transitions from Hodgkin's disease to leukæmia have taken place under the eyes of competent observers, but they are very rare. Only three such cases are on record so far as I know, that of Fleischer and Penzoldt,[1] that of Mosler,[2] and one reported by Senator,[3] where two sisters came under observation, both suffering from Hodgkin's disease. One died of it; in the other the blood changed to that of leukæmia before death.

Doubtless many of the other cases supposed to exemplify a similar transition were really cases in which a leucocytosis arose owing to some inflammatory complication, as not uncommonly occurs (see below, Table XII.).

From the existence of these very rare cases of a transition to leukæmia it has been supposed, especially by French observers, that Hodgkin's disease is simply an early stage of true leukæmia and that this would always become apparent were it not that the patients die of some intercurrent disease before the signs of leukæmia have time to show themselves in the blood. One difficulty with this view is that there occur chronic cases which last from eight to ten years without any change in the blood. Another difficulty is that the transition is in fact rare

[1] Deut. Arch. f. klin. Med., vol. 17.
[2] Ziemssen's "Handbuch d. Path. and Therap.," vol. 8.
[3] Berl. klin. Woch., 1882. p. 533.

despite the relative frequency with which the disease is met with.

(II.) Undoubtedly many cases diagnosed as Hodgkin's disease are in fact cases of glandular hypertrophy due to syphilis or tuberculosis, and this fact has led many to the belief that *all* cases called Hodgkin's disease are in reality only syphilitic or tubercular adenitis. In a considerable number of cases, however, tuberculosis has been disproven by careful inoculation experiments with the glandular tissue, and there is no reasonable doubt that *some* cases at any rate are not due to tuberculosis or syphilis. Probably the diagnosis can never be made with absolute certainty during life.

(III.) The frequent occurrence of fever and other symptoms characteristic of an infectious disease has led some writers to class it as such. In a certain percentage of cases the disease (like leukæmia) has run an acute course, lasting not more than six weeks from the first symptom to death. In some chronic cases the same sort of evidence of an infectious nature has been brought forward. Ulcerations occur in the mouth and intestine through which morbid products might gain admission. Various bacteria (pyogenic and others) have been found in the blood and tissues from time to time, but numerous negative examinations for micro-organisms are also on record, and the evidence is insufficient to establish the infectious nature of the disease. None the less, there is a growing tendency among the leading writers and observers in Germany and elsewhere, to believe that the disease will ultimately be shown to be infectious.

(IV.) Meantime most surgeons continue to regard it as a form of sarcoma and to treat it like malignant disease.

The Blood.

Whatever the nature of the disease, we find in the earlier stages of most cases normal blood, as will be seen in Table XII. (cases 7 to 14 inclusive).

As the disease progresses the hæmoglobin soon begins to fall, later the red cells, until, as at the end of Case 10 of the present series, the blood may reach the severest grade of anæmia. In acute cases the anæmia may develop very rapidly. The usual qualitative changes characterizing severe secondary anæmia may be present.

TABLE XII.—HODGKIN'S DISEASE.

No.	Age.	Sex.	Red cells.	White cells.	Per cent. Hæmoglobin.	Remarks.
1	28	F.	5,500,000	64,000	75	Polynuclear, 95 per cent. Lymphocytes, 5 "
2	....	M.	3,848,000	39,200	48	Acute. Diff.[1] 500. Adult cells, 95.2 per cent. Young " 4.6 "
3	24	F.	4,886,000	32,000	53	
4	19	F.	5,528,000 5,160,000	22,200 25,400	....	Diff. 200 cells. Adult cells, 86.5 per cent. Six weeks later. Young " 12. " Eosinophiles, 1.5 "
5	19	M.	2,480,000	20,200	33	Stained specimens normal.
6	37	M.	5,990,000	13,500	....	Adult cells, 95 per cent. Young " 5 "
7	25	M.	5,440,000	9,500	59	Death; autopsy.
8	19	F.	5,724,000	6,800	42.	Adult cells, 60 per cent. Young " 40 "
9	Adult.	M.	3,652,000	5,800	....	Diff. 300. Adult cells, 50.0 per cent. Young " 45.3 " Eosinophiles, 1.3 " Myelocytes, 1.7 " Big spleen, pallor, nosebleed, debility.
10	29	M.	5,210,000 3,840,000 1,000,000	5,000 5,600		 Two months later. Three weeks "
11	58	M.	2,820,000	4,800	60	Adult cells, 80 per cent. Young " 17 " Eosinophiles, 3 "
12	21	M.	4,560,000	4,000 5,800	....	Re-entry.
13	23	M.	4,210,000	3,332	....	Myelocytes, 1 per cent. Big liver and spleen. Eosinophiles, 4 "
14	....	M.	3,800,000	1,440	67	Diff. 500. Adult cells, 71.25 per cent. Young " 28. " Eosinophiles, .75 " One normoblast.
15	....	..	....	No leucocytosis.	. ...	Diff. 200. Adult cells, 63.5 per cent. Young " 36.5 " Eosinophiles, 1 " Many of the lymphocytes have two nuclei.
16	....	...	..... .	....	....	Diff. 300. Adult cells, 41.7 per cent. Young " 48.4 " Eosinophiles, 9.3 " Myelocytes, .6 "
17	4	M.	....	....	....	Diff. 500. Adult cells, 60.2 " Young " 36. " Eosinophiles, 5.6 " Myelocytes, 2. " Two normoblasts.
18	....	F.	....	....	....	Diff. 500. Adult cells, 92.6 per cent. Young " 5.2 " Myelocytes, 2.2 " No eosinophiles.
19	....	...	....	....	... .	Diff. 313. Adult cells, 62.3 " Young " 37 " Myelocytes, 6 "

White Cells.

When inflammation arises in the glandular tumors and sometimes when none is found, the white cells may be greatly increased, even up to a ratio of 1 : 80 red cells, as in Case 1 of the present series. There is, however, no more resemblance to leukæmia than in any other form of leucocytosis, the adult cells

[1] Diff. =Differential count of.

alone being increased. There is no reason for supposing, as Reinert[1] does, that relative diminution of the young leucocytes is owing to the diseased condition of the lymph glands, for, unless some septic process gets a foothold in the glands, the young cells present a normal number or even (as in Case 16) considerably increased percentages.

As in any other cachectic condition, small numbers of myelocytes may be found. They were seen in six of our cases out of fourteen in which a color analysis was made, the highest percentage being two per cent. Eosinophiles are usually decreased when leucocytosis is present.

Summary.

Normal blood in early stages.
Later often marked anæmia.
Sometimes leucocytosis.

Diagnostic Value.

The only help given us by the blood is in excluding leukæmia. Syphilis, tuberculosis, or malignant disease might cause similar blood changes or lack of changes.

[1] "Die Zählung der Blutkörperchen," Berlin, 1891.

PART II.

ACUTE INFECTIOUS DISEASES.

CHAPTER III.

INFLUENCE OF FEVER ON THE BLOOD.

SOME of the blood-changes found in acute infections are to be regarded as due simply to the fever associated with the disease. It is worth while, therefore, to consider what fever *per se* can do to the blood.

Maragliano[1] and others have shown that during fever from any cause a *contraction* of the peripheral vessels occurs. When fever disappears, whether spontaneously or from the action of antipyretics (phenacetin, quinine, etc.), a *dilatation* of the vessels follows.

Following the laws to which we have so often alluded, the contraction of the vessels causes a concentration of the blood with rise in specific gravity and in the number of blood cells per cubic millimetre. This concentration is still further increased by the greater loss of water which the organism suffers during fever than under normal conditions.

The effect of these two influences in increasing the number of red cells per cubic millimetre is, however, counteracted to a considerable extent by the sharing of the blood in the general tissue destruction which goes on with increased rapidity during fever. Many corpuscles are thus destroyed, but until the temperature falls the anæmia is covered up by the concentration. When the fever leaves the patient there is a sharp fall in the number of cells per cubic millimetre, due partly to the destruction of corpuscles (hitherto masked by concentration) and partly to the *dilution of the blood* which is the result of the post-febrile dilatation of the peripheral vessels above mentioned. The sud-

[1] Zeit. f. klin. Med., vols. 14 and 17.

denness of this fall in the count is proportional to the suddenness of the fall in temperature.

The alkalinity of the blood has been often said to be diminished in fever, but recent research tends to show that these results were obtained by faulty technique, and it is doubtful whether the reaction of the blood shows any constant changes in fever.

Leucocytes and fibrin show no constant changes, though in the majority of infectious fevers they are increased.

PNEUMONIA.

The Blood as a Whole.

(*a*) Bacteriology.—The diplococcus lanceolatus has been found in the blood of pneumonic patients repeatedly, especially in those in whom there has been some secondary diplococcus infection (*e.g.*, diplococcus endocarditis); but such findings are rare and have generally been in fatal cases with very severe generalized infection.

For example, Sittmann [1] out of 16 cases found diplococci in the blood of 6, most of which were complicated with lesions in other organs, and 4 of which died, while of the 10 whose blood was sterile, 9 recovered.

Boulay [2] found the organism in 2 cases shortly before death. Belfanti [3] found it but 6 times out of a large number of cases, and of these 6, 5 died. Goldschneider [4] and Grawitz [5] got similar results. From these facts it appears that the presence of pneumococci in the blood is a bad prognostic sign.

(*b*) Coagulation is remarkably rapid and in fresh specimens the fibrin network is very thick and appears within a few minutes.

(*c*) In cases with cyanosis the blood is often concentrated at the periphery so that its specific gravity is high and the number of corpuscles large.

[1] Deut. Archiv f. klin. Med., 1894, p. 323.
[2] Paris Thesis, 1891.
[3] Riforma Medica. Naples. 1890, No. 37.
[4] Deut. med. Woch., 1892, No. 14.
[5] Grawitz: Charité-Annalen. vol. 19.

(*d*) Monti and Berggrün[1] observed that in children the specific gravity was high throughout the course of the disease, falling with the temperature.

Red Cells.—During the fever the red cells are approximately normal (unless increased by cyanosis); but after the crisis there is often slight anæmia, due partly to the blood destruction evidenced by the frequent presence of hydrobilirubin in the urine and the not infrequent occurrence of jaundice. Grawitz considers also that a general relaxation of the peripheral vessels in the post-critical period causes a dilution of the blood with (apparent) lessening of the red cells.

Maragliano has noticed "degenerative" changes in the red cells in severe cases, but as a rule they do not appear much affected either in quantity or quality and our attention is chiefly directed to the

White Corpuscles.—1. Probably as early as the time of the chill, and certainly within a few hours after it, the leucocytes are greatly increased, and continue so throughout the febrile period.

2. There is no correspondence between the daily variations in temperature and the leucocyte curve. In cases in which a pseudo-crisis occurs (the temperature falling but quickly rising again), the leucocyte count remains high, while at the time of the true crisis and often a few hours before it the leucocytes *begin* to fall. This fall, however, is hardly ever by "crisis," but though starting perhaps a little before the temperature it is one to two days longer in reaching normal. When the temperature reaches normal by lysis the leucocytes fall with it but generally more slowly, and reach normal later.

3. When resolution is delayed the leucocytosis continues, sometimes for weeks, and very gradually sags down to normal in cases in which resolution eventually occurs without complication. If abscess, empyema, or gangrene follow, the leucocytes stay up.

4. The degree of leucocytosis is probably the resultant of the factors mentioned on page 91, and does not run parallel to the degree of fever or the amount of lung involved. Nevertheless cases with extensive signs in both lungs are more apt to have very high counts, provided the "reaction" of the patient

[1] Arch. f. Kinderheilk., vol. 17.

against the infection is vigorous. The cases appear to fall into the following groups as regards the degree of leucocytosis present.

1. Mild infection, vigorous reaction = slight leucocytosis.
2. Severe or moderate infection, vigorous reaction = marked leucocytosis.
3. Severe infection, feeble reaction = no leucocytosis.

(*a*) The cases in Class 1 all recover, but they are very few in number. (*b*) Those in Class 2, which includes over nine-tenths of all cases, may or may not recover, according as the fight between patient and disease comes out one way or the other.

(*c*) Class 3 *almost invariably die*; there is not sufficient of a struggle to raise the leucocyte-count.

Where either the patient or his disease *easily* gains the mastery there is no leucocytosis or a very slight one; but in the much larger class of cases in which the struggle is a fierce one, leucocytosis appears, *whichever way the struggle results.*

Pick[1] noted that pneumonia complicating cases of small-pox which were already very sick, caused no leucocytosis, and the same is often true in those whose power of resistance is reduced by age, alcoholism, typhoid, or by some chronic disease.

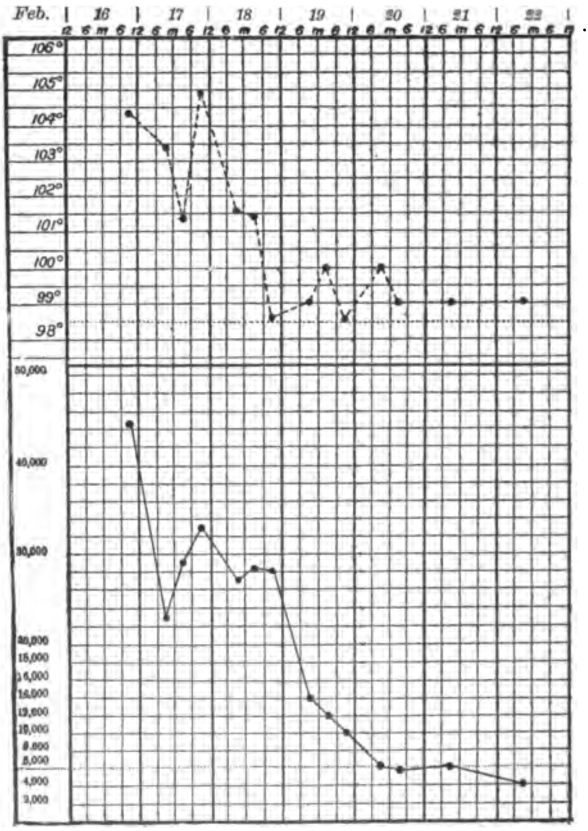
Von Jaksch, noticing the fatality of cases without leucocytosis, suggested that we should induce leucocytosis by injecting turpentine or other irritants so as to cause abscess; but this has not proved of any benefit to the patient, nor has the production of leucocytosis without abscess, as can be done with pilocarpine or nuclein, been any more successful. There is no difficulty in producing the leucocytosis by these means, but all observers are agreed that it does the patients no good.

Leucocytosis is checked by antipyretics (Hare[2]) but not by cold bathing, which speaks in favor of the latter method of reducing temperature.

The general course of the leucocytes is seen in the accompanying charts from Billings, to whose excellent article I am greatly indebted.

[1] Arch. f. Dermat. und Syph., vol. 25, p. 63.
[2] New York Medical Record, May 9th, 1896.

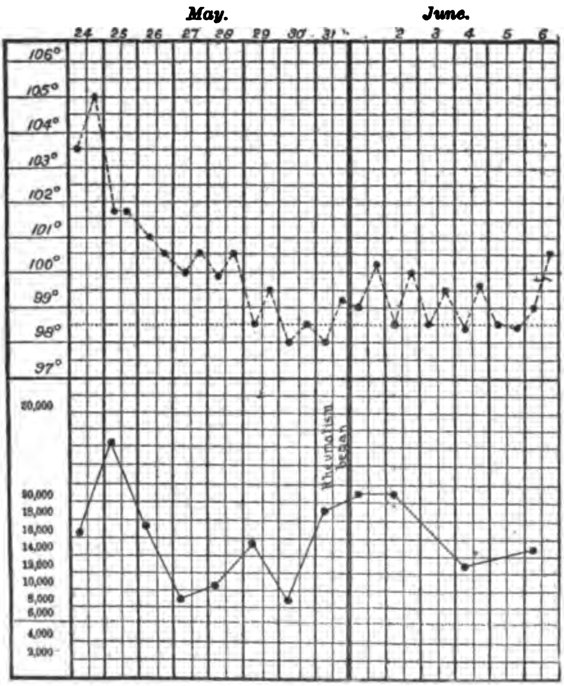
CHART I.—PNEUMONIA, SHOWING FALL BY CRISIS (BILLINGS).



The upper chart shows the course of the temperature, the lower that of the leucocytes.

Qualitative Changes.—As in most forms of leucocytosis the adult leucocytes are enormously increased, often making over ninety per cent of all the white cells. Eosinophiles and blood plates disappear and the young forms are much reduced. After the crisis this is reversed, the adult forms falling often below sixty per cent, while the eosinophiles and blood plates are above normal. As to the differential count in the (fatal) cases in which

CHART II.—PNEUMONIA AND RHEUMATISM.



The upper chart shows the course of the temperature, the lower that of the leucocytes.

leucocytosis is absent, data are scanty. Bieganski thought the adult varieties decreased, Rieder found them increased, while Billings finds them normal. No general law can be stated on this point as yet.

In one remarkable case occurring at the Massachusetts General Hospital in 1894, the conditions were entirely different form those just stated. The patient, a girl of six, had at entrance 72,100 leucocytes per cubic millimetre. Two days after the count was 94,600. A differential count made at the same time showed that the small lymphocytes made up sixty-six per cent of all the 94,600 leucocytes per cubic millimetre. The adult cells were reduced to thirty per cent. Lymphatic leukæmia was thought of, but the leucocytosis was gone in ten

days and within a fortnight the patient left the hospital well. I have seen one reference to such a condition. "In a certain number of cases the leucocytosis is characterized by the great number of the youngest forms of leucocytes. This condition persists during convalescence."[1]

Diagnostic and Prognostic Value.

1. In cases of so-called "*central pneumonia*" in which the symptoms but not the physical signs of the disease are manifest, the presence of a well-marked leucocytosis is often of great diagnostic value. It excludes malaria, typhoid, and uncomplicated grippe as causes of fever, and if scarlet fever and suppuration can be excluded by other evidence, it makes pneumonia very probable.

I have repeatedly seen the diagnosis of pneumonia made in the absence of physical signs and largely on the evidence of the blood count, the diagnosis being confirmed several days later by the appearance of typical signs of consolidation. In a case of Dr. F. C. Shattuck's, sick five days, yet showing no signs of consolidation of the lung, the presence of a marked leucocytosis excluded typhoid, the only other likely diagnosis, and led Dr. Shattuck to treat the case as pneumonia, the wisdom of which course was later demonstrated by the appearance of signs of consolidation.

2. Between pneumonia and capillary bronchitis the condition of the blood is of no help, as the latter also causes leucocytosis, and some cases affecting the larger tubes do the same.

3. In cases of pneumonia occurring in very old or very young people, in which the fever and symptoms may be very slight, the presence of leucocytosis may be the first thing to direct our attention to the lungs, dyspnœa and cough being absent.

In *prognosis*, the important point is that *the absence of leucocytosis is a very bad sign, while its presence is neither good nor bad.* It must be remembered also that in the very mildest cases we may find the same absence of leucocytosis which in any other but the mildest would be almost surely fatal.

[1] Stiènon: Jour. de Méd., de Chirurg. et de Pharm., Bruxelles, 1895, t. iv., fasc. 1.

This last point, which appears to me of great importance, is illustrated by the following figures:

Halla reported 14 cases; 2 had no leucocytosis, and both died.

Billings reported 22 cases; 1 had no leucocytosis and died.

Laehr with 16 cases, and Rieder with 26, got similar results.

Ewing in 101 cases found leucocytosis absent in 6; 6 died.

Von Jaksch and Kilodse likewise maintain that the absence of leucocytosis is usually fatal.

In the Massachusetts General Hospital 229 cases have been studied. In general they entirely confirm the results obtained by Billings and summarized above; 18 of these presented no leucocytosis at any time, and of these 18, 17 died and the other one seemed moribund but finally recovered.

The evidence, therefore, is overwhelmingly in favor of the view that where leucocytosis is absent in any but the mildest cases the prognosis is almost fatal. The presence of leucocytosis, on the other hand, is no guaranty whatever of a favorable issue.

The series of cases at the Massachusetts Hospital is too large to exhibit in tabular form. Their results may be summarized as follows:

Cases with leucocytosis between	10,000 to 15,000 =	24
" " " "	15,000 " 20,000 =	49
" " " "	20,000 " 25,000 =	46
" " " "	25,000 " 30,000 =	31
" " " "	30,000 " 35,000 =	19
" " " "	35,000 " 40,000 =	4
" " " "	40,000 " 45,000 =	7
" " " "	45,000 " 50,000 =	2
" " " "	50,000 " 55,000 =	4
" " " but not accurately counted =		43
	Average = 24,000 +	229

TYPHOID FEVER.

Bacteriology.

Although the bacilli of Eberth are occasionally to be found in the blood by culture, it is only in the most marked cases that they occur, and then but rarely, so that at present we derive no help in doubtful cases by the bacteriological examination of the blood.

Toward the end of the disease, when the temperature is apt to be very irregular (so-called "period of steep curves"), pyogenic cocci are occasionally to be found in cultures made from the blood, and doubtless account for many of the recrudescences and temporary febrile attacks, with or without chills, which are so common in early convalescence.

The Blood as a Whole.—1. Coagulation and fibrin are normal.

2. Specific gravity follows the course of the hæmoglobin.

3. The general effects of fever (see above, page 158) are in part accountable for the changes next to be described, while some of them are more peculiar to typhoid fever.

Red Cells.—During the first two weeks there are no considerable changes, except in so far as a certain amount of concentration of the blood with apparent increase of cells may be brought about by diarrhœa or sweating. Baths have a like effect if the blood is examined just after the immersion.[1] In the third week the red cells usually begin to decrease and in extreme cases may get as low as 1,300,000 at the beginning of convalescence—*i.e.*, when body weight begins to increase. Hayem considers that the diminution begins rather suddenly in the middle or end of the third week of severe cases, but according to Thayer the diminution is gradual, though at first slight, growing more rapid at the time of defervescence, and continuing often into convalescence. The lowest point is reached about the first week of convalescence.

The following figures (Thayer) illustrate this.

First week, 2 counts.	Second week, 10 counts.	Third week, 9 counts.	Fourth week, 6 counts.	Fifth week, 7 counts.	Sixth week.
5,636,000	4,960,599	4,951,535	4,038,333	3,856,786	4,364,250

His later counts show a gradual increase. He finds that the amount of anæmia bears, *as a rule*, a direct relation to the severity of the case, but in one of his cases a grave anæmia (1,300,000) followed a mild attack. "The anæmia may be severe enough to form of itself a dangerous complication of the process."

Hæmoglobin.—The loss of coloring matter roughly parallels that of the red cells, but is always relatively greater and is slower in reaching normal.

[1] Antipyrin and acetanilid have no effects on the red cells.

Leucocytes.—The absence of any increase of the white cells is the most important point.

Starting with an approximately normal count, the number falls during the fever, often below 2,000, according to Hayem, and sometimes below 1,000 per cubic millimetre. Khetagurow finds the lowest counts (2,500–3,000) about the end of the third week.

Thayer's figures are as follows:

First week, 21 counts.	Second week, 50 counts.	Third week, 40 counts.	Fourth week. 28 counts.	Fifth week, 16 counts.	Sixth week, 5 counts.
6,984	6,468	6,260	5,877	6,621	7,000

In the two hundred and ninety-two cases counted at the Massachusetts General Hospital, the course of the leucocytes has unfortunately not been followed by weeks with sufficient accuracy to make comparisons of value. In a general way, however, they corroborate all of Thayer's positions. At the beginning of the cases the count was often high (11,000), owing probably to concentration of the blood by starvation and diarrhœa. The high count of *red* cells confirmed this, the ratio of red to white remaining normal. The counts of leucocytes then gradually diminished, as in Thayer's cases.

The range of the counts was as follows:

Between	1,000 and	2,000 =	7	cases.
"	2,000 "	3,000 =	25	"
"	3,000 "	4,000 =	28	"
"	4,000 "	5,000 =	52	"
"	5,000 "	6,000 =	44	"
"	6,000 "	7,000 =	50	"
"	7,000 "	8,000 =	28	"
"	8,000 "	9,000 =	25	"
"	9,000 "	10,000 =	22	"
"	10,000 "	11,000 =	7	"
Over	11,000.........	=	4	"
			292	cases.

From these figures I have excluded all cases counted only under circumstances likely to concentrate the blood (cyanosis, after baths, after severe diarrhœa).

There is no doubt that leucocytosis *does* occasionally occur when no complication exists *so far as we can ascertain during life*. The four cases over 11,000 (see the above table) were all

counted repeatedly and complications were carefully sought for, but none were found. The most striking case showed the following counts:

October	3d	13,100
"	4th	13,000
"	5th	16,500
"	7th	13,300
"	8th	11,200
"	10th	10,600
"	13th	13,500
"	15th	17,700
"	17th	15,500, death; autopsy.

The autopsy showed typical typhoid lesions and nothing else.[1] Another and much milder case showed 11,000–12,000 white cells constantly for over two weeks, and no cause could be found to account for it.

The great rarity of such cases and constant association of leucocytosis with any of the numerous complications which we can recognize, rather inclines me to the belief that in all the cases in which leucocytosis exists constantly, some complication really *is* present though unrecognized. The possibility of a secondary septic infection, of an osteomyelitis, or phlebitis of internal veins cannot be excluded without further evidence.

Examples of the effect of complications are as follows:

Perforation.—Case I.	(*a*)	Five days before perforation,	8,300
	(*b*)	At time of the perforation,	24,000
Case II.		At time of perforation,	18,500
Phlebitis.—Case I.	(*a*)	Two days before onset,	6,400
	(*b*)	At time of the onset,	12,900
	(*c*)	One week later,	10,100
Case II.	(*a*)	One week before onset,	4,800
	(*b*)	At time of onset,	16,200
Otitis Media.—Case I.	(*a*)	At entrance,	5,300
	(*b*)	Mastoid abscess,	16,400
Case II.	(*a*)	At entrance,	8,400
	(*b*)	Two weeks later, after opening drum membrane (sero-purulent discharge),	11,200

[1] Thrombosis of internal veins and osteomyelitis were not carefully searched for at autopsy and may have existed.

Case III.	(a) At entrance, ...	7,320
	(b) Otitis, ...	14,000

A freely discharging otitis soon ceases to cause leucocytosis, *e.g.*, a case of serous otitis media seven days after puncture, but still freely discharged, showed but 5,320 white cells per cubic millimetre.

An abscess of the buttock raised the count from 8,000 to 11,200, and a hemorrhage from 8,000 to 11,300.

General bronchitis has usually no effect in augmenting the leucocyte count unless the disease invades the smallest tubes (capillary bronchitis). Thus two cases of this affection showed 9,000 and 8,000 leucocytes respectively.

Cystitis had no effect in two cases.

In two cases whose symptoms simulated otitis (deafness, rise of temperature, pain in the head, and in one a convulsion) but whose blood counts were normal, the trouble turned out to be functional and nothing came of it, the symptoms disappearing within twenty-four hours.

Some observers [1] have noted a slight leucocytosis at the beginning of convalescence. Thayer did not find this, and I have been equally unsuccessful.

It occasionally happens in very exhausted patients that complications fail to produce any leucocytosis, the patient (as in some fatal cases of pneumonia or purulent peritonitis) being unable to react against the infection. For example, I have seen a large ischio-rectal abscess develop in a moribund typhoid patient without producing any effect on the leucocyte count. Von Limbeck has noticed the same lack of reaction in typhoid patients after a hemorrhage and bronchopneumonia, and Rieder in croupous pneumonia occurring as a complication.

These cases, however, are exceptional, and in many of them the percentage of adult leucocytes rises, though no increase in the total leucocyte count is present. This increased percentage of adult forms generally betrays the presence of the complication, since during most of the disease (if uncomplicated) the adult forms are *diminished*.

In normal cases the blood begins to return to normal as

[1] *E.g.*, Aporti and Radaeli (11th Congress for Medical Science, Rome, March 29th, 1894).

soon as the fever is gone and reaches the normal in the sixth or seventh week.

Qualitative Changes.

Red Cells.—The condition is either normal or shows the changes common to all varieties of secondary anæmia.

White Cells.—All observers are agreed upon the following changes:

1. The adult cells progressively diminish with a corresponding increase in the young cells. This change is but slight in the first two weeks, but grows marked in the latter part of the illness, the adult cells falling below fifty per cent. Among the young cells the larger forms predominate.

2. It is not until after the disappearance of fever (from three to ten days after it, according to Ouskow) that the adult cells begin to increase again and their normal percentage is not reached untill the tenth or eleventh week. Thayer's differential counts show:

Second week, 5 counts.	Third week, 1 count.	Fourth week, 3 counts.	Fifth week. 1 count.	Sixth week, 2 counts.
71.7 per cent.	66.5 per cent.	65.3 per cent.	58.5 per cent.	53.4 per cent.

3. Eosinophiles are present in small numbers.

Summary.

1. Post-febrile anæmia, sometimes very intense.
2. No leucocytosis; in late weeks leucopenia.
3. Increased percentage of young leucocytes at the expense of adult forms, especially marked in later weeks.
4. Most complications cause leucocytosis.

Diagnostic Value.

There are few diseases (outside of those known as diseases of the blood itself) in which the blood count is so often of value in diagnosis. The diagnosis of typhoid fever is to be made by exclusion—exclusion of other causes of fever and of local inflammatory processes in particular.

1. Now in this process of exclusion, the blood is a most powerful adjuvant, inasmuch as almost all *local inflammatory processes have leucocytosis, while typhoid* (uncomplicated) *does not.*

I have seen two cases in which the chart and symptoms pointed to typhoid but in which the persistent marked leucocytosis directed attention to the search for an inflammatory focus. Both were at first unattended with pain, tenderness, or other localizing symptom, but later signs and symptoms began to point to the *liver*, from which pus was evacuated by puncture. These cases of *abscess of the liver* are typical of the value of blood examination for any deep-seated suppuration. I have seen good clinicians puzzled for twenty-four hours over the diagnosis between appendicitis and typhoid, but the indication of the blood count was always fulfilled. All pyæmic or septicæmic processes are distinguishable from typhoid by the same test—the presence of leucocytosis in the former.

Of the value of the blood in distinguishing certain cases of pneumonia from typhoid I have already spoken on page 165.

2. Aside from local or general pyogenic infections perhaps the disease most often confounded with typhoid is *malaria*. This is especially the case in the southern part of this country, where for want of proper blood examination the confusion of the two diseases is indicated in such a term as "typho-malarial fever." Malaria and typhoid are alike in having no leucocytosis, but the presence of the malarial parasite is an absolute test and in marked cases is always decisive. Very mild cases of malaria may show so few organisms in the peripheral circulation that without prolonged search they cannot be found, and in the severest types of all, the organisms are not very abundant. In the vast majority of cases, however, the organism can be readily found and our diagnosis made certain.

3. Tuberculosis, if uncomplicated by any pyogenic organisms, cannot be distinguished from typhoid by the examination of the blood alone, as neither disease shows leucocytosis.

A large proportion of young leucocytes is commoner in typhoid than in tuberculosis, but it may occur in either disease. In the majority of cases, however, tuberculosis is complicated with septicæmia from a secondary pyogenic infection, and is then easily distinguished by the existence of leucocytosis.

4. *Typhus fever* has not been well studied and the reports of its blood condition are contradictory. At present we cannot say whether or not it can be distinguished from typhoid by the blood examination.

The occurrence of complications in typhoid may mask its characteristic blood changes so as to make the blood useless in diagnosis; but in most early cases, in which the diagnosis is especially important and difficult, the blood shows no leucocytosis and is therefore of great value in the exclusion of other diseases.

DIPHTHERIA.

Bacilli of diphtheria in the circulating blood are practically never to be found.

The specific gravity, according to Grawitz, is *above* normal at the height of the disease. He obtained the same result experimentally by injecting cultures of the Klebs-Löffler bacillus into dogs and rabbits. He concludes that the poison of the disease is lymphagogic and so concentrates the blood.

Red Corpuscles.—Morse's[1] investigations show an average of 5,100,000 in twenty cases counted during the first week of the disease and of 5,150,000 in 10 cases during the second and third week of the disease—practically normal figures.

These are the first systematic[2] investigations of the red cells in diphtheria and are confirmed by the reports of Ewing, Engel, and Billings. The latter observer in counts made in seven cases during the first five days of illness found an average of 5,600,000+ red cells per cubic millimetre. During the first five to ten days after this, the same cases showed an average loss of 510,000 cells per cubic millimetre; five out of the seven showing considerable losses, two remaining about the same. These were cases treated without antitoxin. The two cases showing no loss of red cells were both very mild, one having no membrane at any time. The diminution ranged from 470,000 (third day) to 2,040,000 (sixth day). As a rule no diminution can be made out until after the third or fourth day.

Out of twenty-three cases treated with antitoxin and each counted several times over, only three showed any considerable diminution in the red cells and these lost less than 400,000 each, not much beyond the limit of error (200,000) allowed for by the investigator, and all of them severe cases. Six patients who were anæmic when admitted (average=4,640,000) showed a

[1] Boston Medical and Surgical Journal, March 7th, 1895.

[2] Earlier reports are faulty as to technique.

steady *rise* in the red cells as the disease (treated with antitoxin) progressed.

It is evident from these figures that antitoxin largely prevents the anæmia which usually develops in the first five to ten days. In cases not treated with antitoxin the regeneration from the resulting anæmia is slow. Healthy individuals injected with antitoxin showed a very moderate reduction in the red cells in about one-half the cases, the greatest loss being 932,000 per cubic millimetre (fifteen cases counted by Billings).

Qualitative Changes.—Billings' careful study of stained specimens showed no deformities in size or shape and no nucleated red cells. Polychromatophilic red corpuscles were very few in the cases in which antitoxin was used, but more numerous where it was not used.

Hæmoglobin.—Here again the most thorough investigations are those of Billings. In cases treated without antitoxin there was an average loss of ten per cent, regained in part during convalescence, but as usual reaching normal later than the count of corpuscles. When antitoxin was given, the diminution of hæmoglobin was less marked, but where the decrease did occur the return to normal was slow compared to that of the red cells, even when the patients were up and about and apparently well.

White Corpuscles.—Leaving out the older observations in which the technique was probably faulty, the principal investigators are Morse, Ewing, Gabritschewsky, and Billings.

All agree that a considerable leucocytosis is present in most cases—34 out of 36 of Billings' cases, 26 out of 30 of Morse's (the latter made but one count in each case), 49 out of 53 of Ewing's. In a general way, the severest cases show the greatest leucocytosis, but it does not follow the pulse, temperature, nor the extent of the membrane, and "the ordinary clinical examination of the patient is of much greater value in . . . prognosis . . . than any information to be gained from the examination of the blood. The latter is simply confirmatory, never indispensable" (Billings). Morse's conclusions are the same, although he considers that with notable exceptions the amount of membrane is a rough measure of the degree of leucocytosis. He finds no correspondence between the glandular swellings and the degree of leucocytosis, though he noted that "in the fatal 'septic' cases with greatly enlarged glands," very high counts were present.

Other cases with little or no enlargement of glands showed equally high counts, however.

Ewing's 4 cases without leucocytosis were all mild, but of Billings' 2 cases without leucocytosis one was the severest of his whole series, while the other was mild. Of Morse's 4 cases without leucocytosis 3 were mild and 1 severe. Gabritschewsky's 14 cases all showed leucocytosis.

Putting the results of these four observers together we see that when leucocytosis is absent the cases are *either* very mild or very severe, conditions analogous to those to be noted in pneumonia and septicæmia. The counts in recent epidemics range from normal to 48,000 (Morse) or to 38,600 (Billings). Felsenthal[1] found 148,229 per cubic millimetre in one case, and Bouchut's[2] counts are often over 75,000.

In a general way the counts rise while the disease progresses and fall gradually as improvement goes on, disappearing after the membrane. "The leucocytosis is well marked by the third day and very likely earlier" (Morse). Billings found an increase after one day's illness, but usually less than was present later in the disease; one of his cases, however, had a higher count on the first day of the disease than on any subsequent day, though no antitoxin was given.

The injection of antitoxin has apparently no effect upon the leucocyte count (strange to say) except in the first twenty-four hours after its use. Immediately, *i.e.*, within thirty minutes after an injection, the leucocytes are stated by Ewing to be considerably diminished, but the leucocyte curve does not reach normal any sooner than in cases in which no antitoxin is given, although it begins to fall in the majority of cases after the injection. The same thing (according to Billings) takes place without antitoxin.

The leucocytes of healthy persons are likewise unaffected by antitoxin injections.

Qualitative Changes.—All authors agree that in most cases the adult forms are increased. Morse found an average of 80 per cent in 26 of his 30 cases. Of the other 4, 1 was normal and 3 subnormal (58, 59, and 59 per cent); 2 of these were con-

[1] Archiv f. Kinderheilk., vol. xv., p. 78, 1893.

[2] Comptes Rendus, 1877, lxxv., No. 3.

valescent, the other had been sick a week and had 12,000 white cells per cubic millimetre. A similar lymphocytosis was present in 1 of Ewing's 53 cases, and in 1 of Rieder's during convalescence. Billings thinks such a lymphocytosis may be present in perfect health, mentioning cases with 32, 33, and 35 per cent of small lymphocytes in sound persons. Such a condition did not occur in any of his diphtheritic cases except in the single fatal case without leucocytosis. Here the adult cells were reduced to 55 per cent and the lymphocytes (large and small) made up the remaining 45 per cent, 28 per cent being large forms.[1] In the rest of his cases the adult varieties averaged 80 per cent and the young forms 19 per cent, the eosinophiles being reduced to 1 per cent on the average and often being entirely absent. With Morse eosinophiles averaged 2 per cent.

The proportion of adult cells is usually directly proportional to the total increase of leucocytes.

Ewing thinks that "the staining reaction of the leucocytes is an accurate measure of the severity of the diphtheritic infection," and this staining reaction he finds increased in favorable cases by the injection of antitoxin.

Billings did not find any such changes in "staining reaction," though he carefully followed out Ewing's procedures.

Engel[2] found that antitoxin at first slightly increased the percentage of young leucocytes, and sometimes this increase was very marked. In one case the young forms increased from twenty-four to sixty-five per cent after antitoxin.

The point on which he specially insists is the presence of considerable numbers of *myelocytes* in fatal cases.

Of the 32 cases examined by him 15 died, and 7 of these had from 3.6 to 16.8 per cent of myelocytes in every one hundred leucocytes. Myelocytes were also present in some of the cases which recovered, but in smaller numbers (1.3 to 1.5 per cent.)

In one case he found on the third day of the disease 4.3 per cent of myelocytes, and from this point the percentage gradually rose to 13.8 per cent, and then fell, there being 1.7 per cent present at the time of death. An abscess occurring in the case

[1] In Rieder's case above referred to, aged three years, the young cells rose from nineteen per cent during the fever to sixty-four per cent in convalescence.

[2] Soc. f. inner. Med., Berlin, July 6th, 1896.

showed only the usual adult leucocytes (polymorphonuclear) in its contents. He concluded that a large percentage of myelocytes is a bad prognostic sign in any case.

Myelocytes are not mentioned in any of the numerous differential counts made by Gabritschewsky, Ewing, Morse, and Billings, so that Engel's observation is so far unique.

Summary.

1. Moderate anæmia, especially in cases treated without antitoxin. Regeneration is slow.
2. Leucocytosis, very roughly parallel to the severity of the disease, unaffected by antitoxin treatment, gradually decreasing as the disease passes off, sometimes absent in very mild or very severe cases.
3. Adult leucocytes much increased during febrile stages, often diminished in convalescence.
4. Myelocytes numerous in some severe cases.

The blood examination has no diagnostic value so far as I can see; in prognosis the absence of leucocytosis (except in obviously mild cases) and the presence of many myelocytes are apparently bad signs.

CHAPTER IV.

ACUTE INFECTIOUS DISEASES (CONTINUED).

SCARLET FEVER.

HEUBNER[1] noted hæmoglobinæmia in one case. Fibrin is not increased even at the height of the fever, provided inflammatory complications are absent.

Red Cells.—Very little is to be found in literature upon the subject. Kotschetkoff[2] noted a gradual diminution of the red cells to about 3,000,000, regeneration taking place in the course of not less than six weeks. Other observers have found little or no anæmia.

Hayem[3] estimates the average loss of red cells at 1,000,000. In mild cases he finds the lowest figures on the first day of normal temperature. In severer cases in which the fever comes down slowly, the red cells may not reach their minimum till twenty-four hours after reaching the normal temperature.

Felsenthal[4] in six cases found the count to be 4,500,000 to 5,500,000—no considerable variation from normal.

Zappert[5] in six cases found it to be from 3,920,000 to 4,500,000, an average of 4,150,000.

White Cells.—Most observers are agreed that *leucocytosis is the rule,* contrasting in this respect with measles, in which no leucocytosis occurs. The increase may be present even six days before the rash appears and attains its maximum two or three days after the eruption. In light cases it may sink to normal even before the fever is gone, while in severer cases it may persist *several days after a normal temperature is reached.* Von Limbeck had a case in which the leucocytosis persisted for

[1] Deut. Arch. f. klin. Med., vol. 23.
[2] Ref. in Petersburg. med. Woch., 1892, 1.
[3] *Loc. cit.*, p. 914.
[4] Arch. f. Kinderheilk., 1892, p. 80.
[5] Zeit. f. klin. Med., 1893, p. 292.

twelve days after the temperature had become normal. Forty thousand per cubic millimetre is not unusual in well-marked cases. Rieder's ten cases averaged 17,500; Felsenthal's six counts were between 18,000 and 30,000.

In a general way the severest cases are apt to have the highest leucocyte counts; the figures have no direct relation to the amount of fever, glandular swelling, or to complications in the ear or kidney.

Qualitative Changes.—The adult forms are increased, often to ninety per cent, soon falling except in the worst cases. The peculiar characteristic of the disease is the persistence of eosinophiles in all but the severest cases despite the increase of adult forms. They may run as high as five per cent during the fever, and are still more numerous in convalescence, remaining increased for six weeks. According to Kotschetkoff, disappearance of eosinophiles is a bad prognostic sign except at the very beginning of the fever, when they may be temporarily absent in favorable cases. Presumably they have some connection with the exanthem, eosinophilia being so common in connection with skin lesions. They may number fifteen per cent of the leucocytes in convalescence. Felsenthal's average is five per cent.; Zappert's, three per cent. The young cells are decreased proportionately to the severity of the case, the worst cases showing only two to four per cent.

An increase of eosinophiles during a scarlatinal nephritis is regarded by Neusser and his pupils as a favorable sign, and their absence as ominous. In ordinary cases without nephritis they reach their maximum in the second or third week and are not normal till the sixth.

Summary.

Moderate anæmia.

Leucocytosis beginning before the eruption and often lasting into convalescence.

Eosinophiles increased in favorable cases, absent in bad cases.

Diagnostic and Prognostic Value.

1. The chief importance of the blood examination is in distinguishing the disease from measles and the eruptions of other diseases. Measles has no leucocytosis.

2. Whether the prognostic significance attached by Neusser and others to the percentage of eosinophiles is genuine or not cannot as yet be positively stated.

MEASLES.

In mild cases the blood shows no changes at all. Where bronchitis, coryza, and conjunctivitis are very marked, fibrin may be increased.

Red Cells.—In mild cases no change—never over 400,000 or 500,000 red cells are lost (Hayem). Felsenthal's eight cases showed counts of 5,000,000 to 5,500,000.

White Cells.—In most cases there is no increase. Felsenthal in eight cases found the count normal or diminished. Pée found but 4,000 in a case with a fever of 102.7°. Rieder's eight cases averaged 7,500, being *lowest* at the height of the disease and increasing as fever passed off. Complication with catarrhal pneumonia or a very bad bronchitis and coryza may slightly raise the count. The eosinophiles, contrary to the example of scarlet fever, are often absent during fever.

The Massachusetts Hospital records furnish the following counts:

	Red cells.	White cells.	Percentage hæmoglobin.	Remarks.
Case 1........	....	6,000	....	Eruption out 1 day.
" 2........	....	6,500	....	" " 3 days.
" 3........	5,000,000	7,000	60	" just out.
" 4........	4,700,000	9,000	65	Petechial eruption ("black measles").

Felsenthal found the adult cells much increased and eosinophiles never over one per cent. I have seen no other full differential counts in the disease. The *value* of the blood examination is considerable in excluding scarlet fever, diphtheria, and syphilitic roseola, all of which show leucocytosis. It cannot apparently be distinguished by the blood count from *Rötheln* (German measles) in two cases of which, seen at the Massachusetts Hospital, the white cells were 6,000 and 8,000 respectively.

A single case of *mumps* showed no leucocytosis.

SMALL-POX (VARIOLA).

Red Cells.—According to Hayem no other fever is so destructive of red cells. During the fever the count is normal or increased, but when the temperature falls permanently the number of red cells falls suddenly, whether because the blood is diluted (see above, page 158) or by a real destruction. From this time on the cells are slowly regenerated; even at the fifteenth day Hayem found them considerably below normal.

In hemorrhagic cases the anæmia comes on more quickly, its degree depending on the amount of hemorrhage. In one case, dying on the seventh day of the eruption, Hayem found but 2,000,000 red cells, in another at the same stage, 4,600,000.

Fibrin is not increased until the stage of suppuration is reached.

White Corpuscles.—Pick, who carefully studied 42 cases, found that the very lightest cases, such as occur in vaccinated persons, may cause no leucocytosis. In a woman of twenty-two on the third day of illness with a temperature of 105°, the count was only 4,200 and on the fifth day (temperature 99°) 3,600. This patient had been vaccinated.

Severe cases if without complication show no leucocytosis till the pus appears in the vesicles, and after this period the leucocytosis slowly sinks again. For example, on the fifth day of the illness, leucocytes 4,200; at the beginning of suppuration, 11,600 (eighth day); at the height of suppuration (tenth day), 17,200; at the thirteenth day, pustules drying up, leucocytes 7,600.

In the severest types, the leucocytes follow about the same course, there being no leucocytosis whatever in the initial or eruptive stages. Only when the infection with pus organisms begins do the leucocytes rise, the poison of variola itself having apparently no tendency to increase the count. The amount and duration of the increase at the stage of suppuration is in a general way proportional to the severity of the case.

ACUTE ARTICULAR RHEUMATISM.

According to Hayem and Garrod [1] the blood constitutes as in syphilis a most valuable measure of the intensity of the sickness,

[1] British Medical Journal, May 28th, 1892.

which is parallel to the severity of the blood-changes rather than to the number of joints affected. The fever, the intensity of the lesions, and the state of the blood run parallel, in a general way, but the degree of anæmia is a more delicate index of the patient's condition than even the temperature chart (Garrod).

The Blood as a Whole.

Fibrin is greatly increased. In no other disease except in pneumonia is the network thicker or more rapid in formation. According to Maclagan, this is to be explained by an increase of tissue metamorphosis. Coagulation, on the other hand, is not quicker but slower than usual.

Lactic acid is present in excess, but cannot be clinically estimated, nor is its excess peculiar to this disease.

The alkalinity of the blood had been reported diminished, but the technique is not considered reliable by the best observers.

Red Cells.—Hayem [1] and Osler [2] state that the poison of acute rheumatism is a powerful and rapid destroyer of red cells. In acute cases, according to Hayem, the red cells lose at least 1,000,000 of their number and in cases which drag along and relapse the loss is from 1,500,000 to 2,000,000. When an attack is cut short by salicylate treatment the drain on the corpuscles is stopped.

So far as can be judged from the figures in Table XIII. of the Massachusetts Hospital cases this diminution does not seem to occur in all cases. Many of these cases had been sick some weeks before the time when the count was made, yet the counts are not very low. In the eight cases which have been sick over twenty days, the average of red cells is 4,462,000; in those sick between one and twenty days, 4,540,000; and in the whole group of cases, 4,400,000. The lowest count was 3,608,000. According to Hayem 4,000,000 is the usual count in acute cases and 3,000,000 to 3,500,000 in those which drag on and relapse.

Qualitative Changes.—Maragliano's so-called degenerative changes in the red cells have been observed in this disease, but are not very marked. Deformities and nucleated corpuscles appear only when the anæmia is very marked.

Hæmoglobin.—As in all secondary anæmias the corpuscles get thin and pale before they die, and hence the coloring matter

[1] *Loc. cit.*, p. 917. [2] "Practice of Medicine," 1895.

is diminished more than the count. The average hæmoglobin percentage in this series is sixty-seven, and the color index .76. Hayem noted that, in some cases during convalescence, as the red corpuscles slowly increase the color index remains low or even goes lower still.

Leucocytes.—All observers agree that leucocytosis is the rule and that its degree is roughly parallel to the acuteness and severity of the attack (the individual's vigor of reaction is always a factor) and the amount of fever. The following tables illustrate the variations of the leucocytes in a fairly typical way:

TABLE XIII., A.—ACUTE ARTICULAR RHEUMATISM.

No.	Age.	Sex.	Duration.	Degree of inflammation.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	50	F.	17 days.	Red and hot.	?	39,000	65	
2	21	M.	5 weeks.	?	4,160,000	31,500	65	Knees and 1 ankle.
3	59	F.	?	?	5,476,000	27,000	94	Patient pale.
4	Adult.	M.	?	?	?	25,900	?	
5	33	M.	2 weeks.	Red and hot.	4,852,000	24,500	76	
6	20	F.	?	?	?	22,400	?	Acute endocarditis also.
7	Adult.	M.	?	?	4,216,000	21,000	56	
8	23	M.	4 weeks.	Tender and hot.	5,192,000	18,300	70	Temperature 102°.
9	28	M.	3 "	?	?	17,800	?	Many joints affected.
10	19	M.	4 days.	Red and hot.	?	17,400	?	
11	49	M.	?	?	4,800,000	17,700	?	Paronychia also.
12	49	M.	?	?	?	17,100	?	Dec. 2d.
13	21	F.	?	Red and hot.	3,944,000	17,000	45	Cheeks rosy.
14	24	M.	2 days.	?	4,600,000	16,000	68	
15	24	M.	?	?	4,670,000	15,500	68	
16	35	M.	....	.....	....	15,200	45	
17	18	F.	1 day.	Red and hot.	4,880,000	15,200	65	Temperature 102°.
18	12	M.	2 weeks.	" "	4,400,000	15,000	56	
19	19	M.	4 days.	" "	4,760,000	14,500	75	Severe case.
20	9	F.	?	?	4,240,000	14,386	60	
21	9	F.	"	Red and hot.	?	14,050	?	
22	47	M.	1 day.	" "	4,750,000	14,000	72	One joint only affected.
23	25	F.	3 days.	Tender and hot.	4,850,000	14,000	75	
24	18	F.	2 months	No redness or heat.	4,156,000	14,000	54	
25	19	M.	?	?	4,172,000	14,000	70	
26	19	M.	?	?	4,580,000	13,500	64	Nov. 10th, 1895.
27	21	F.	1 day.	Red and hot.	?	13,500	?	
28	29	M.	?	?	4,320,000	12,750	68	
29	?	?	?	?	4,128,000	12,650	65	Dec. 1st, 1895.
30	37	F.	1 month.	Swollen, tender.	5,320,000	12,500	64	
31	23	M.	?	" "	5,000,000	12,500	65	
32	32	M.	?	?	?	12,100	?	Purpura also.
33	30	F.	?	?	4,160,0 0	12 000	?	
34	47	M.	4 weeks.	Very slight.	4,288,000	12,000	65	
35	27	F.	3 days.	Not " "	3,880,000	11,600	65	
36	17	M.	1 week.	" " "	4,600,000	11,500	70	Mild case.
37	27	M.	10 days.	Hot and red.	4,200,000	11,500	60	
38	33	M.	4 weeks.	?	5,480,000	11,000	80	Hands alone involved.
39	18	M.	?	Not red and hot.	?	10,000	....	One joint only affected.
40	28	M.	3 weeks.	" " "	3,608,000	7,000	40	
41	Adult.	M.	?	?	3,768,000	6,800	....	
42	29	M.	9 weeks.	Some joints hot.	4,104,000	5,500	58	Fourth relapse.
43	30	F.	?	?	3,440,000	4,700	26	Specific gravity 1040.
				Average =	4,400,000+	16,800+	67	

TABLE XIII., B.—SUBACUTE ARTICULAR RHEUMATISM.

No	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	
1	25	M.	4,750,000	15,000	60	
2	30	F.	4,644,000	13,000	63	
3	28	F.	?	10,600	?	
4	28	F.	4,684,000	8,000	75	
5	Adult.	M.	4,016,000	6,200	41	
6	"	F.	4,188,000	5,750	73	
	Ave	rage =	4,400,000	9,760	62	

TABLE XIII., C.—CHRONIC RHEUMATISM, CHIEFLY ARTICULAR.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	
1	78	F.	?	7,200	?	
2	19	F.	5,248,000	8,300	45	
3	32	F.	?	6,400	?	
4	58	M.	4,744,000	6,500	60	
5	30	F.	?	6,100	?	
6	20	M.	5,576,000	9,800	62	
			Average =	7,400		

TABLE XIII., D.—MUSCULAR RHEUMATISM.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	46	M.	4,580,000	7,500	70	
2	54	M.	4,360,000	7,500	75	
3	38	M.	?	6,600	?	
4	54	M.	3,820,000	14,000	58	During febrile attacks.
5	27	F.	?	6,000	?	Lumbago.
6	35	M.	?	5,700	"	"
			Average =	7,500+		

The average leucocytosis in the acute cases is 16,800; in those mild and more chronic, so-called "*subacute*" cases the leucocytes range lower, averaging 9,760; while in chronic rheumatism, whether articular or muscular (including lumbago), there is no increase at all (average =7,450).

Summary.

Anæmia with leucocytosis, the degree of which is a measure of the severity of the infection. Fibrin much increased.

Diagnostic Value.

The blood tells us little if anything that could not be learned in other ways. It does not differ at all from that of a *septic arthritis*, or from that of acute *gonorrhœal arthritis*.

The only cases that I remember in which a blood examination has been valuable are the following:

CASE I.—The patient had muscular pains, fever, and a history of a malarial attack some months earlier. The question to be decided by the blood examination was between malaria and "rheumatism." The leucocytes were 23,600 per cubic millimetre, which made it clear that the case was *neither* malaria nor "rheumatism," since the former never increases the leucocytes and the latter could only give so high a count in case genuine *articular* inflammation were present. The case turned out to be croupous pneumonia which the high leucocyte count strongly suggested.

CASE II.—Patient presented symptoms and signs of acute polyarticular rheumatism with fever. The fever came down under salicylates, but soon rose again, and the man became wildly delirious. His delirium persisted after the salicylate was stopped. Several joints continued swollen and tender. The fever was very moderate, ranging between 99° and 101°. There were no rose spots and no spleen. The question arose as to whether it was a case of sepsis with localization in the joints, or whether it was a case of typhoid supervening on an arthritis of some kind. The blood count, which was repeated several times, always showed a perfectly normal blood except for a slight anæmia. The subsequent course of the case, during which he remained for nearly three weeks more or less delirious, made it clear to Dr. F. C. Shattuck, under whose care the patient was, that the diagnosis was typhoid.

Chronic rheumatism (muscular or articular) produces no constant blood changes appreciable by clinical methods (see Table XIII., C and D).

ASIATIC CHOLERA.

In no other disease so far as I am aware has an *acid reaction* in the blood been reported. This is at the end of

life. All observers agree that the alkalinity is at least greatly reduced.

Our knowledge of the corpuscles is best summed up in Biernacki's [1] study of thirty-eight cases.

Red Cells.—In the *stadium algidum*, or stage of collapse, most of the symptoms are due to the great concentration of the blood from the loss of serous fluid in the stools. Hayem found the increase of red cells from this concentration to amount to from 1,000,000 to 1,500,000 per cubic millimetre.

Biernacki [1] found 7,662,500 in one case twenty-four hours after the beginning of the disease. The specific gravity may be as high as 1071 or 1072.

White Cells.—Leucocytosis is present, not merely as the result of concentration, but as a genuine increase to at least double the normal count. Biernacki found that cases with particularly high counts (40,000 to 60,000) were soon fatal, so that he considers a marked leucocytosis in the algid stage as a bad prognostic sign, although patients also die with low leucocyte counts in this period. Such a leucocytosis does not occur in ordinary diarrhœa or dysentery.

Leucocytosis is present as early as twelve hours from the first symptom and lasts at least as late as the sixth day. In the stage of reaction it usually decreases. In one very mild case reported by Biernacki there was not only no increase, but leucopenia (4,375 per cubic millimetre).

The differential count shows from eighty-two to ninety-five per cent of adult cells and a corresponding diminution of the young forms.

ERYSIPELAS.

Halla, Pée, Reinert, Rieder, and v. Limbeck agree that leucocytosis is usually present in well-marked cases. Von Limbeck finds the "leucocyte curve" to run roughly parallel with the temperature chart, sometimes beginning to fall a little before the latter. The counts rarely run very high, yet Reinert counted 39,627 in one case. Pée noted that the leucocyte count increases only while the process is spreading and that the size

[1] Deut. med. Woch., 1895, No. 48.

of the count was a tolerably accurate measure of the severity of the case.

Rieder found in seven cases an average of only 15,000 per cubic millimetre despite very high temperatures. In one case the leucocyte count remained high after the temperature had fallen, but in the others it anticipated the temperature. In one mild case he found no leucocytosis. Adult cells are greatly increased as in other forms of leucocytosis. Hayem noticed the same dependence of the leucocyte count upon the severity of the process.

In five cases at the Massachusetts General Hospital I found 17,000, 14,000, 12,700, 7,250, and 6,200, the last two very mild cases. The count of leucocytes seemed proportional to the severity of the affection.

When the disease occurred in "scrofulous" cases, Hayem found only 7,000–8,000 leucocytes per cubic millimetre, while in cases with very extensive process and high fever 12,000–20,000 were present. He found also a loss of 500,000–1,000,000 in the count of the red cells, according to the severity of the case. This showed itself particularly just before the fall of the temperature. I have seen no reference by other writers to the condition of the red cells in this affection.

TONSILLITIS (FOLLICULAR).

Halla,[1] Pick,[2] and Pée[3] found leucocytosis as a rule in uncomplicated follicular tonsillitis; Rieder found it in a case complicated with acute nephritis.

The following table confirms these observations in the main, though in mild cases no leucocytosis was present.

The blood examination has no diagnostic value so far as I am aware. It is worth knowing that a simple tonsillitis can cause leucocytosis, to the end that if such is discovered on blood examination we need not suppose that some other process is present to account for the increase.

[1] Zeitschrift f. Heilkunde, 1883, p. 198.
[2] Prag. med. Woch., 1890, p. 303.
[3] Pée: Inaug. Dissert., Berlin, 1890, p. 8.

TABLE XIV.—TONSILLITIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo-globin.	Remarks.
1	30	F.	4,750,000	16,000	80	Temperature 101°.
2	27	M.	4,556,000	15,500	67	Six days; slight.
3	Adult.	F.	4,860,000	14,000	..	Follicular.
4	30	M.	4,730,000	13,500	76	Convalescent.
5	24	F.	5,000,000	13,500	68	Follicular.
6	Adult.	M.	....	13,500		
7	..	M.	4,952,000	12,250	94	
8	24	F.	5,816,000	11,900	65	Streptococcus; slight articular rheumatism.
9	..	M.	5,000,000	11,800	90	Follicular.
10	19	F.	4,552,000	11,600	52	
11	18	M.	5,150,000	11,500	83	Chronic recurrent; out in two days.
12	22	F.	5,016,000	9,600		
13	Adult.	F.	4,200,000	5,800	60	Follicular.
14	23	F.	....	7,925	52	Follicular; slight; temperature 99° next day.

GRIPPE.

The references in literature to the blood of grippe are very scanty. Orion (*Archiv. d. Méd. milit.*, 1890, p. 280) found fibrin increased during the early days of the disease. Rieder (*Münch. med. Woch.*, 1892, XXXIX.) found no leucocytosis in grippe and but little in the "catarrhal pneumonia" following it.

In the following table it is evident that the red cells are not perceptibly affected and that the leucocytes remain normal in at least three-quarters of the cases. Only seven of the thirty cases showed leucocytosis, and in one or more of these some complication was very possibly present. This is of importance in excluding *pneumonia* and *local inflammatory* conditions. The blood does not help us to distinguish the disease from *typhoid*. From malaria it may be distinguished by the absence of malarial organisms. In one case (No. 30, Table XV.) after an operation for traumatic epilepsy, the temperature rose to 104°, with a chill, and the question of meningitis was considered. The absence of leucocytosis excluded the meningitis and the attack turned out to be grippe, which was just then very prevalent.

TABLE XV.—GRIPPE.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	37	M.	....	14,200	..	13th, coarse râles in both chests; chlorides diminished.
				9,200	..	15th.
2	Adult.	M.	4,840,000	14,400	..	And bronchitis.
3	35	M.	5,111,200	12,800	97	Pharyngitis; cough; considerable sputa; constipated.
4	36	F.	4,771,700	12,100	..	With pharyngitis.
5	Adult.	F.	4,644,000	12,000	62	
6	32	F.	3,850,000	11,500	85	
7	27	F.	....	11,100	..	
8	50	F.	....	10,900	..	Fine râles and increased voice sounds.
9	19	F.	5,720,000	10,400	..	11th, hysteria (?); temperature, 105°.
			5,192,000	7,600	57	27th, 30th, chill; cyanosis; weak rapid pulse; 82 per cent of adult cells; autopsy.
10	19	M.	....	10,300		
11	Adult.	M.	4,950,000	10,000		
12	35	M.	....	9,900		
13	40	M.	5,904,000	9,400	..	Subacute laryngitis.
14	..	F.	4,860,000	9,200		
15	Adult.	F.	4,900,000	9,000		
16	31	M.	5,310,000	9,000		
17	32	F.	4,200,000	8,000	25	
18	23	M.	5,500,000	7,400		
19	25	M.	5,616,000	6,800		
20	Adult.	M.	4,240,000	6,800	..	With dry pleurisy.
21	42	M.	5,856,000	6,000		
22	24	M.	4,952,000	6,000		
23	Adult.	M.	4,559,000	5,600		
24	30	M.	....	5,500		
25	Adult.	M.	5,600,000	4,600		
26	44	M.	5,685,000	4,550		
27	31	M.	5,424,000	4,000		
28	Adult.	M.	5,260,000	3,500		
29	30	F.	5,488,000	3,144		
30	..	..	....	2,600	..	Temperature 104°; ten days after a head operation; question of meningitis.

SEPTICÆMIA.

Puerperal septicæmia, infected wounds, septic arthritis, septic endocarditis, general infections with pyogenic bacteria, "pyæmia," are all identical so far as their effects on the blood are concerned, and will be considered together under the general head of Septicæmia.

Bacteriology of the Blood.

Cocci can be demonstrated in cultures from the blood of septicæmia more frequently than in any other class of infections. Rosenbach[1] in 1884 found streptococci and staphylococci in sepsis. Garré[2] in 1885 found the last-named coccus in a case of osteomyelitis. In 1890 v. Eiselsberg[3] found staphylococci in ten cases of septic wounds and one case of osteomyelitis, and streptococci and staphylococci together in five more cases whose wounds had become septic.

Czerniewsky,[4] Stern and Hirschler[5] found the same organisms in puerperal fever, the former observer in five cases.

Brunner,[6] Hoff,[7] and Blum[8] found pyogenic staphylococci in pyæmia and sepsis, and Saenger,[9] Roux and Lannois,[10] Cantu,[11] and Bommers[12] had equal success, each in a single case.

Canon[13] and Sittmann[14] investigated large numbers of cases with many positive results, and Grawitz[15] and Petruschky[16] were successful in finding pyogenic cocci in the blood of cases of ulcerative endocarditis as well as in other septic infections.

Taking the results of all these investigators together, it seems evident that in the majority of cases of septicæmia, blood cultures, taken according to the directions on page 35, show the presence of pyogenic organisms, and that in many obscure septic cases the diagnosis may be greatly facilitated by such an examination. Negative results are of course very far from excluding

[1] "Microorganismen b. d. Wundinfectionskrankheiten," etc., Wiesbaden, 1884.

[2] Fortsch. d. Med., 1885, No. 6.

[3] Wien. klin. Woch., 1890, No. 30.

[4] Archiv f. Gynäkol., 1888, No. 33.

[5] Wien. med. Presse, 1888, No. 28.

[6] Wien. klin. Woch., 1891, No. 20.

[7] Dissert., Strassburg, 1890.

[8] Münch. med. Woch., 1893, No. 16.

[9] Deut. med. Woch., 1889, No. 8.

[10] Revue de Méd., 1890, No. 12.

[11] Rif. Med., 1892, No. 96.

[12] Deut. med. Woch., 1893, No. 16.

[13] Deut. Zeit. f. Chirurg., 1893, p. 571.

[14] Deut. Arch. f. klin. Med., 1894, p. 573.

[15] Charité-Annalen, 1894, vol. 19.

[16] Zeit. f. Hygiene, 1894, pp. 59 and 413.

septicæmia, but positive ones are sometimes of great value if proper precautions are taken in the technique of the examination. In the diagnosis of malignant endocarditis, often a most difficult one, Grawitz thinks blood cultures are especially important and likely to prove positive when the disease is present (see Diseases of the Heart, page 255).

Red Cells.—All observers agree that very marked anæmia is present in severe cases. Roscher's[1] investigations tend to show that the diminution in red cells in septicæmia is greater than in any other infective disease, and appears in a shorter time. He found such a diminution present no longer than a few hours from the beginning of the illness. He finds the amount of anæmia proportional to the severity of the case, and (reckoning by means of the estimated solid residue) concludes that whenever the blood has lost one-quarter of its substance or more, death follows. He considers, therefore, that help as to prognosis is given us by the blood examination in septicæmia.

The serum becomes very watery, partaking of the general atrophy of the blood tissue. In a case of intensely acute puerperal sepsis Grawitz found the red cells reduced to 300,000 (!) although the patient had been sick less than twenty-four hours. The case seems almost incredible, but is reported in great detail in the author's recent text-book, to which reference has so frequently been made. He accounts for it by the combination of blood destruction and dilution.

In the nine cases of puerperal sepsis seen at the Massachusetts General Hospital in recent years the red cells averaged 3,780,000, which is very low, considering the shortness of the illness in most cases. (The influence of hemorrhage during parturition must of course be taken into account.)

In most of the septic wounds which I have seen the counts have not been low. But in one case of septicæmia from a suppurating fibroid of the uterus the red cells numbered only 1,800,000.

The *hæmoglobin* is usually diminished about as much as the corpuscles. According to Bond it tends to crystallize about the edge of a slide and cover-glass preparation of the fresh blood.

Deformities in the shape and size of the corpuscles are not usually present except in the severest cases.

[1] Inaug. Dissert., Berlin, 1894.

TABLE XVI.—PUERPERAL SEPTICÆMIA.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	21	F.	2,300,000	26,000		
2	29	F.	3,900,000	23,900	68	Two days before delivery.
				21,000	..	Day of delivery.
				9,500	..	One day after delivery.
				15,500	..	Five days after delivery; breasts caked.
				15,000	..	Ten days after delivery.
				11,800	..	Twenty-six days after delivery.
3	28	F.	3,784,000	22,000	55	Miscarriage five days before; septic; curetted.
				13,600	..	Three days later, temperature falling.
				8,300	..	Seven days later, temperature normal.
				15,800	..	Fourteen days later, temperature up; curetted again.
				14,900	..	Fifteen days later, temperature falling.
				15,000	..	Sixteen days later, temperature falling.
				9,500	..	Thirty-two days later, temperature falling.
4	25	F.	2,936,000	20,000	50	April 1st, 1894.
				21,000	..	" 3d, 1894.
5	32	F.	4,904,000	19,300	..	Curetted.
				9,300	..	One week later, well.
6	24	F.	3,556,000	18,400		
7	..	F.	....	Marked increase.	..	Adult cells, 94%; young cells, 6%.
8	19	F.	....	9,000	..	Curetted the day before.
9	26	F.	5,368,000	5,600	..	Died.

Hæmoglobinæmia with reddish staining of the serum is often noticeable in the dried and stained cover-glass specimen where the plasma is deeply stained.

Leucocytes.—Considerable controversy has taken place as to the changes in the white cells effected by septicæmia; some observers finding leucocytosis, while others find none.

The results of experimental infections referred to above (see page 95) and the parallelism of the leucocyte changes in pneumonia, peritonitis, and diphtheria fully explain these apparent divergences, which perfectly exemplify the rules stated on page 91.

Leucocytosis occurs only when the struggle between the patient and his disease is intense, and whichever is victorious.

When either side wins without any difficulty, *i.e.*, in the mildest and in the severest cases, leucocytosis is nearly or entirely absent; indeed, leucopenia may be found (as for instance in a case of septic endometritis reported by v. Limbeck—only 3,000 leucocytes). Von Limbeck and Krebs[1] found no leucocytosis in cases of perpetual septicæmia, but these were all fatal cases or very mild ones. Rieder, on the other hand, and the great majority of other observers (Sadler,[2] Roscher,[3] Kanthak,[4] Grawitz, etc.) find leucocytosis. This means that in most cases observed by these writers the infection was of moderate severity.

Only two of the twenty-one cases in Tables XVI. and XVII. showed no leucocytosis. One was very mild, the other died on the day of the count.

TABLE XVII., A.—SEPTIC WOUNDS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	37	F.	5,880,000	48,400	....	Sloughing breast; bedsore.
2	28	M.	7,600,000	25,400	....	Septic wound of foot.
3	31	F.	5,680,000	15,300	....	Sloughing breast after cancer
				6,700	....	operation.
			5,840,000	23,200	....	One month later; wound clean.
4	27	M.	4,450,000	10,500	....	Septic hand.
5	..	M.	5,600,000	8,800	....	Septic finger.

TABLE XVII., B.—SEPTICÆMIA WITH ARTHRITIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	8	M.	....	25,000	....	Pus in elbow joint; no injury.
				43,000	....	Two days after operation, vent not free; opened further.
				24,000	....	Seven days after operation.
				20,700	....	Eight days after operation.
				6,700	....	Sixteen days after, well.
2	34	M.	4,520,000	19,000	65	Gonorrhœal, pus in knee.
3	59	M.	....	18,500	....	Pus in shoulder joint, no trauma.
4	22	M.	....	13,800	....	Gonorrhœal ankle.
5	39	M.	....	8,940	....	Gonorrhœal ankle; cultures negative.

[1] Krebs: Dissert., Berlin, 1893.

[2] Sadler: *Loc. cit.*

[3] Roscher: Dissert., Berlin, 1894.

[4] Kanthak: Brit. Med. Journal, June, 1892.

TABLE XVII., C.—GENERAL STREPTOCOCCUS SEPTICÆMIA.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo-globin.	Remarks.
1	Adult.	M.	5,248,000	41,400		
2	"	F.	1,800,000	46,000	....	Suppurating fibroid.

Summary.

1. Rapid development of severe anæmia.
2. Leucocytosis marked, except in very mild or very severe cases.
3. Blood cultures often contain pyogenic cocci.

Diagnostic Value.

The advantage of a positive bacteriological examination is obvious. Of the value of the blood count in distinguishing septic from non-septic wounds and estimating the degree of sepsis and the importance or needlessness of operative interference, not much is known. The subject deserves to be carefully worked out from a surgical point of view. The following cases, however, tend to show that we might utilize blood counting far more than we do to determine questions of this sort:

CASE I.—Frank B—— was a case of appendicitis operated on by Dr. M. H. Richardson at the end of an attack. A little pus was found, the appendix was excised, and the wound nearly closed, a small strand of gauze, however, being left in. Several days after the operation, there being at the time no external discharge, the temperature rose. The wound seemed perfectly clean. The man was very nervous about himself, and much stirred up at each dressing; and as the temperature never went higher than 101°, there seemed to be considerable doubt as to what the cause of the temperature was. The blood count in this case showed 52,000 leucocytes. On opening the wound a large amount of broken-down blood clot was evacuated, and the temperature came down to normal.

CASE II.—Mrs. S—— was a case of pus tube shelled out and sewed up tight. Ten days after the operation the temperature began to look as if pus were present. Here again the patient

was exceedingly nervous; and, as so often happens, the question was asked and re-asked, whether she was keeping up her own temperature by the state of her mind. The blood count, however, showed marked leucocytosis, which led to a careful ether examination, revealing a fluctuating mass behind the uterus, from which pus was obtained by puncture.

CASE III.—Mr. R—— entered the Massachusetts General Hospital in December, under the service of Dr. C. B. Porter, with a compound fracture of the thigh. Some days after it had been put up, the temperature began to suggest the presence of pus, the wound, however, remaining perfectly clean. I counted the blood, and found a marked leucocytosis. A more thorough exploration of the wound revealed a pocket of pus, the evacuation of which brought down the temperature. I was not sure in this case whether the absorption of the blood clot, such as takes place, I suppose, after any compound fracture, would be sufficient to cause leucocytosis. I therefore counted several cases in which there was fever and presumably blood-clot absorption, namely, a hæmothorax, a pelvic hæmatocele, two compound fractures, and a crushed foot; in none of these was any leucocytosis present.

CASE IV.—Mr. S—— was operated on by Dr. J. C. Warren for traumatic epilepsy. Nothing special was found, and the wound was closed. Ten days after the operation the temperature rose to 104°, and the patient complained of severe headache and pain in the back. I counted the blood, and found no leucocytosis. Next day the temperature was down. The patient apparently had the grippe.

Several cases in which an old malaria was supposed to be "brought out" by a surgical operation, the patient having irregular fever and chills after the operation, have shown, on examination of the blood by the writer, no malarial organisms but marked leucocytosis. In these cases the symptoms of "malaria" ceased when the wound was more thoroughly drained, and I have no doubt that many cases of "malaria" after surgical operations are really wound sepsis.

It is difficult to make inferences from a leucocytosis in such cases, because no one, so far as I know, has thoroughly investigated the blood condition during the normal healing process of wounds. But there are certainly many cases in which we need the kind of information about the condition of a wound which the blood might give us, if the changes in connection with wounds were better known.

How often the questions are asked: Is this patient septic? Does this temperature mean anything of importance? Is this wound well drained? Is this complaint of pain hysterical or does it mean something operable?

How often the blood count would help us to answer such questions without leaving it for time to settle them after the most urgent need of settling them is gone, we do not yet know.

In puerperal cases, the fact that leucocytosis is always present for several days after delivery makes it harder to judge from the blood whether a given case is septic. I doubt if the blood count will give any information on this point not to be more easily obtained in other ways. Blood cultures, if positive, are of far greater importance, but take more time.

ABSCESS.

The effects of abscess upon the blood are, I suppose, due to septicæmia. Nevertheless septicæmia *with* abscess formation differs enough from septicæmia *without* abscess formation, both clinically and hæmatologically, to make a separate description convenient.

The most easily studied variety of abscess is that connected with appendicitis, inasmuch as the frequency of operations in such cases gives us opportunity to verify what we suppose to be indicated by the blood count and see how far our suppositions are true.

At the Massachusetts General Hospital, most patients with other varieties of abscess go straight to the surgeon and their blood is not examined, but many cases of appendicitis come first to the medical wards, and hence we have records of over eighty cases whose blood has been examined.

I shall therefore begin the description of the blood in abscess by an account of appendicitis, which may probably be considered a typical case of abscess formation.

APPENDICITIS.

After excluding all cases in which the diagnosis was not sure we have left seventy-two cases.

TABLE XVIII.—APPENDICITIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent haemoglobin.	Remarks.
1	43	M.	3,400,000	52,000	....	Question of typhoid; pus found at operation.
2	40	M.	6,800,000	43,000	....	Chronic case; 96 per cent. of adult leucocytes.
3	30	F.	....	39,900		
4	..	....	5,184,000	36,800		
5	..	....	4,800,000	36,000		
6	50	M.	4,290,000	35,000		
7	..	....	6,000,000	34,000	....	Three days after operation.
8	..	....	6,500,000	34,000	....	Seven " " "
9	?	M.	5,072,000	28,000		
10	..	....	....	24,200	....	Second attack; operation at 11 P.M. November 5th, count at 5:30.
				16,850	....	Serous peritonitis found. November 6th, 5 P.M.
				15,600	....	November 7th, 3 P.M.
				10,700	....	" 8th, 4 "
				15,100	....	Temperature still up. November 9th, 5 P.M.
				14,600	....	November 10th, 5:30 P.M.
				11,800	....	" 11th, 8:30 "
				17,850	....	" 12th, 8:30 "
				18,200	....	" 13th, 8 A.M.
				13,100	....	" 13th, 8:30 P.M.
						Recovery complete ten days later.
11	..	....	....	24,000	....	24° September 1st; operation, free turbid fluid without adhesions.
				12,500	....	September 10th.
				19,500	....	" 12th; pocket of pus found.
12	23	M.	5,200,000	24,000		
13	..	....	5,144,000	23,000	82	January 14th.
				16,100	....	" 15th; before operation, ℥v. + pus.
14	..	M.	....	22,500	....	Not operated; entrance.
				13,000	....	Second day.
				9,500	....	Third "
15	..	M.	....	22,300	....	12:20 operated; belly full of pus.
				9,500	....	8:30 moribund; blood dark and hard to get.
16	35	F.	....	22,000	....	July 6th.
				19,400	....	" 8th.
				14,900	....	" 10th, 104°; recovery.
17	..	M.	....	21,900	....	Appendicitis eight to nine days; operation; post-cæcal abscess.
18	..	....	....	21,700	....	November 5th, first operation.
				21,400	....	" 10th.
				16,000	....	" 13th.
				24,400	....	" 15th.
				20,200	....	" 16th.
				47,700	....	" 19th, second operation (pus pocket).
				16,700	....	" 20th.
				13,000	....	" 21st.
				10,700	....	" 22d.
				30,300	....	" 26th, third operation (pus pocket).
				20,900	....	" 27th.
				17,700	....	" 28th.
				25,100	....	" 29th.
				28,100	....	" 30th.
				20,400	....	December 1st.
				15,400	....	" 2d.
				25,000	....	" 3d.
				11,900	....	" 4th.
				15,600	....	" 5th.
				21,900	....	" 6th.
				19,000	....	" 7th.
				11,900	....	" 8th.
				12,800	....	" 9th.
				11,700	....	" 10th.
				12,300	....	" 11th.
				15,600	....	" 12th.
				13,400	....	" 13th.
				14,700	....	" 21st.
				16,500	....	" 25th.
				11,300	....	" 26th
19	31	M.	... .	20,540	....	October 5th.

TABLE XVIII.—APPENDICITIS (*Continued*).

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo-globin.	Remarks.
19	31	M.	....	33,000	....	October 6th.
				14,640	....	" 8th.
				9,200	....	" 9th; moved bowels.
				21,000	....	12th; tender still and tense.
				24,900	....	99° to 100° temperature.
				13,700	....	Normal; still sore.
20	..	M.	....	....	....	Appendicitis twenty-four hours; resistant belly.
				20,100	....	October 23d.
				14,000	....	" 24th, 9 A.M.
				12,400	....	" 24th, 4 P.M.
				13,250	....	" 24th, 11 P.M.; not operated.
				8,750	....	" 25th, 8 A.M.; liquids every two hours.
				9,600	....	" 25th, 8 P.M.
21	24	F.	....	20,000	....	May 24th.
				19,000	....	" 25th.
22	..	....	....	20,000	....	June 5th; temperature, 101.4°; pain and vomiting.
				9,000	....	June 7th; no pain.
				10,000	....	" 8th; no pain; temperature, 100.6°; discharged.
23	..	....	4,800,000	20,000	....	Operated; pus.
24	..	....	5,564,000	20,000		
25	..	....	4,670,000	19,750	....	January 13th.
			5,296,000	15,000	....	" 15th.
26	20	F.	....	19,600	....	" 29th.
			4,680,000	12,000	....	February 1st.
			4,668,000	8,933	....	" 5th; after operation.
27	..	....	....	19,500	....	No operation.
28	58	M.	5,120,000	19,000	....	Purulent peritonitis.
29	20	M.	5,680,000	18,980		
30	14	M.	....	18,000		
31	..	....	....	17,500	....	Accident case; operation; pint of pus under pressure.
32	25	M.	....	16,250	....	Fifth day. November 7th.
				17,450	....	November 8th.
				12,000	....	" 11th; not operated; well on 17th.
33	25	M.	....	16,200		
34	..	....	....	16,200	....	Eighth day; operation; large abscess cavity.
35	40	F.	....	16,051	....	Operated.
36	..	....	....	16,000	....	Entrance.
				8,000	....	Same evening; no operation.
				7,500	....	Next day.
				6,800	....	" "
37	..	....	6,160,000	16,000	....	General peritonitis.
38	..	....	....	16,000	....	November 12th, noon.
				8,000	....	" 12th, 8:30 P.M.
				7,500	....	" 13th, 8 A.M.; not operated.
				6,600	....	" 13th, 8 P.M.
39	..	....	8,300,000	16,000		
40	17	M.	4,380,000	15,600	66	March 25th, 9 P.M.; vomiting, pain, tenderness.
				19,500	....	" 27th; comfortable, no vomiting; signs more localized.
				22,900	....	" 28th; slight tenderness only.
				35,300	....	" 29th; bowels move well; no symptoms.
				32,800	....	" 30th; operation; large amount of pus.
41	27	M.	4,330,000	15,523		
42	23	M.	5,910,000	15,330		
43	22	M.	....	14,800	....	20th; general peritonitis.
				10,000	....	21st; " "
44	..	.. .	....	14,700	....	Five days; third attack; operation; free turbid fluid, no perforation; prompt recovery.
45	36	F.	4,250,000	14,700	70	27th, 8 P.M.
				13,150	....	28th; symptoms less; no operation.
46	23	F.	....	14,400	....	February 23d, } ℥ ij. foul pus.
				10,300	....	" 24th, }
47	..	....	4,960,000	14,000	....	Catarrhal.
48	..	....	....	13,400	....	3 P.M., November 9th; appendicitis twenty-four hours.
				11,200	....	5 P.M., November 10th; temperature, 98.8°.
49	..	. ..	5,000,000	13,000		
50	..	....	....	13,000	....	Visible tumor. March 27th.
				17,000	....	" " April 26th, operated; pus.
51	..	....	4,626,000	12,000		

TABLE XVIII.—APPENDICITIS (*Continued*).

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
52	..	M.	....	12,000	....	Appendicitis cake. August 3d, operation; gangrenous appendix with adhesions.
				16,900	....	August 6th, fæcal fistula.
53	..	M.	....	11,900	....	No symptoms except pain for twenty-four hours; not operated.
54	51	M.	....	11,800	....	Very slight tenderness; no resistance or dulness. July 6th.
				19,900	....	Temperature up; tenderness and resistance. July 7th, operation; pus found.
				11,700	58	December 28th, 4 P.M.
55	..	M.	4,860,000	17,600	....	" 30th, 10 A.M.
				16,670	....	" 31st, 11 "
				11,950	....	January 1st, 9 P.M.
				10,800	....	" 5th.
				10,875	....	July 27th; nine days pain and vomiting.
56	22	F.	4,664,000	21,000	....	July 28th: more pain, tenderness and vomiting: operation showed pus.
				10 700	....	November 7th, appendicitis six days.
57	..	M.	....	9,000	....	Operation: abscess with considerable pus; gangrenous perforated appendix with concretion in it.
				10,500	....	Not operated till later.
58	12	F.	3,690,000	10,400	....	February 6th, 12 M.; slight pain and tenderness.
59	46	M.	....	9,800	....	" 7th, 3 P.M.; temperature dropping.
				10,400	....	Catarrhal.
60	..	...	5,600,000	10,500	....	"
				10,140	....	One week, fourth attack; no cake, no acute symptoms;
61	..	M.	....			operation; no pus.
				10,040	....	Sixth day, operation; abscess, ℥ i. pus.
62	..	M.	....	9,000	....	Operated: no pus: catarrhal.
63	..	M.	....	8,400	....	December 1st.
64	24	F.	....	10,000	....	" 6th.
				7,200	....	" 15th.
				7,600	....	" 16th.
				7,760	....	No pus.
65	..	....	5,106,000	7,600		
66	..	....	5,600,000	7,600	....	No operation.
67	..	....	6,500,000	7,600	....	No pus.
68	..	. .	6,500,000	7.050	....	Catarrhal appendix; five days in hospital.
69	31	M.	....	7,000	85	Catarrhal appendix.
70	47	M.	6,000,000	6,600	....	" chronic; nearly well; operation; no pus.
71	56	M.	....	6,000	....	" or very slight.
72	22	F.	4,320,000			

From the seventy-two cases of the adjoining table, the following conclusions are to be drawn:

1. Red cells: no changes except in chronic cases with long-standing abscess.

2. Coagulation often slow, but fibrin always increased in suppurating cases.

3. As in most infections the mildest and the severest cases show no leucocytosis. *Four cases with general purulent peritonitis showed no leucocytosis*, its absence being confirmed by repeated examinations. The total absence of leucocytosis in a case not obviously mild is a very bad prognostic sign as in pneumonia and diphtheria.

4. Catarrhal appendicitis is rarely accompanied by leucocytosis (only once in this series—14,000).

5. *An increasing leucocytosis means a spreading process and may be the only evidence of the fact.* In Case 40 of this series, the patient entered with vomiting, localized pain and tenderness. The leucocytosis was 15,600. Three days later he was comfortable, had no vomiting and very little tenderness, and in all respects seemed to be improving, yet the white cells had risen to 22,900. Operation was postponed owing to the lack of all unfavorable symptoms *except the blood count.* Next day the bowels were moving well and the patient *had no fever and no bad symptoms of any kind,* but his leucocytes had risen to 35,300. On the following morning the surgeon was finally persuaded to operate and found a large amount of pus.

A steadily increasing leucocytosis is always a bad sign and should never be disregarded even when (as in this case) other bad symptoms are absent. It is of far more significance than a larger count which does not increase.

6. The size of the leucocytosis is of comparatively little significance. A low count (8,000–11,000) means one of three things:

(*a*) A mild case.

(*b*) A very severe case.

(*c*) An abscess thoroughly walled off.

After the abscess has ceased to spread and has become well walled off, the leucocyte count remains stationary or decreases. If it bursts into the general peritoneal cavity the count may rise sharply or it may fall to normal or subnormal, its movement depending on the degree of resistance which the system offers.

7. In the majority of cases the pus is neither completely walled off nor free in the belly, and such cases are accompanied by a moderate and fluctuating leucocytosis, which rises and falls according to a variety of conditions which cannot be accurately interpreted.

It usually increases in the first three or four days of the illness, and then becomes stationary or declines if the case is taking a favorable course (*i.e.*, if the pus is being absorbed or walled off), while it continues to increase when the case is going on from bad to worse.

Case 20 illustrates the course of the leucocytes in a favorable case not operated on; the leucocytes fell gradually but steadily from hour to hour so that in two days the count came down from 20,100 to 8,750, the tumor and tenderness simultaneously disappeared, and the patient was well in a few days more. Case 38 dropped in eight hours from 16,000 to 8,000 and quickly recovered. In Case 19, the leucocytosis fell in three days from 33,000 to 9,200, but rose again when the bowels were moved by enema, and took some days to reach normal again. Evidently the peristalsis injured the abscess wall so that the process began to spread again and had to be walled off afresh.

8. When a leucocytosis of 18,000–25,000 is maintained for a number of days it usually means a large abscess pretty well walled off.

9. The majority of cases as seen at the Massachusetts General Hospital on the second, third, and fourth day of the illness show leucocytosis of 15,000–24,000, thirty-three of the present series falling within these figures. Counts larger than this have always been proved to mean a large amount of pus or a general peritonitis. Of the cases below 15,000 (fifteen in all) twelve did not come to operation, or if operated showed no pus. This statement excludes the four cases of general purulent peritonitis without leucocytosis mentioned above.

10. Case 18 illustrates several points. After the first operation the leucocyte count did not fall so rapidly as usual, and the cause of this soon turned out to be a pus pocket, after the evacuation of which the count fell in twenty-four hours from 47,700 to 16,700, only to rise again for another accumulation of the same kind.

After this last (third) operation the case progressed slowly but favorably, and yet the leucocyte count remained more or less above normal for a month. The wound was healthy, freely discharging, and had healed satisfactorily at the time of the last count recorded.

Whether all wounds follow this course as regards the leucocytes I do not know. It is an important point which needs working out, namely: What is the normal behavior of the blood count during the healing of granulating wounds? If this were known, we might get valuable information as to whether a wound is doing well or not, by means of the blood count, which,

if septic, would probably behave differently from its wont in wounds which do well. As it is, all these questions are not answerable. It is to be hoped that surgeons will investigate them.

Differential Diagnosis.

1. The presence of a marked leucocytosis excludes simple colic with or without constipation, and excludes certain forms of intestinal obstruction (if uncomplicated). Such cases of intestinal obstruction as are complicated with ulceration or gangrene or due to cancer may raise the leucocyte count.

Between general peritonitis from an appendicitis and intestinal obstruction, the presence of marked leucocytosis points to the former; but its absence may accompany either affection. I remember a case in which the diagnosis lay between these two affections, and operation was delayed because the absence of any leucocytosis was thought to rule out peritonitis, and it was hoped to get the bowels started by enemata, etc. When finally the abdomen was opened stinking pus gushed out and the patient died the same day.

2. Treves[1] has reported several cases in which it was hard to decide whether the diagnosis was typhoid or appendicitis. A blood examination would probably have decided the matter as it has in three cases in the writer's experience. Most cases of appendicitis of any severity show leucocytosis; typhoid almost never does if uncomplicated. Curtis[2] reports a case of typhoid with a tumor and tenderness in the right iliac region which closely simulated appendicitis but turned out to be a floating kidney. The blood count would have decided the matter.

3. Between appendicitis and pus tube the blood gives no help, as both affect it alike.

4. Ovarian or pelvic neuralgia (uncomplicated) never causes leucocytosis and may be excluded by its presence. The same is true of floating kidney, which has been sometimes confounded with appendicitis.

5. Gall-stone colic, and renal colic if uncomplicated by inflammatory disturbance, cause no leucocytosis, and can therefore be distinguished from appendicitis in most cases.

[1] Medico-Chirurgical Transactions, 1888, lxxi., p. 165.
[2] "Twentieth Century Practice of Medicine," vol. viii., p. 461.

If cholangitis, cholecystitis, pyelitis, or severe cystitis complicate the colic, the examination of the blood will be no help to us.

6. *Impaction of fæces* in the cæcum will not cause any leucocytosis and may be excluded when such is present. The count may be of use, it seems to me, in deciding us whether an enema ought to be given. It is sometimes desirable to give an enema in cases simulating appendicitis, to help clear up the diagnosis, but some physicians are afraid to do so for fear of causing a walled-off abscess to break into the general peritoneal cavity. In such cases, if no leucocytosis were present, we might go ahead with a clearer conscience.

Mr. B—— entered the Massachusetts General Hospital September 20th, 1893, with a diagnosis of appendicitis. For twenty days he had been having pain and tenderness in the region of the appendix, pain being controlled by morphine. The bowels had been loose, he said. There was dulness, tenderness, and a distinct tumor in the region of the appendix, with slight pyrexia. The blood count showed only 8,000 leucocytes. He was given a compound cathartic pill, had a large movement of the bowels, and all symptoms and signs disappeared.

7. *Extra-uterine pregnancy* and pelvic hæmatocele may cause leucocytosis like appendicitis, but *do not increase fibrin* unless peritonitis is present, and are likely to *show a marked diminution in red corpuscles* if the hemorrhage is severe. The red cells are normal in appendicitis except in chronic cases with abscess.

8. *Floating kidney* has been already mentioned in Curtis' case, where in combination with typhoid it closely resembled appendicitis. Even without the presence of typhoid, the same difficulty of diagnosis may arise between appendix and floating kidney. The presence of leucocytosis could not be accounted for by the latter.

One of the next most common forms of abscess seen in medical wards is pyosalpinx, which I shall call by the English name of "pus tube." As this produces the same effect on the blood as pelvic abscess or pelvic peritonitis, I shall consider the three processes together.

PUS TUBE, PELVIC ABSCESS, AND PELVIC PERITONITIS.

Almost all that has been said of appendicitis applies equally well to these conditions.

TABLE XIX., A.—PUS TUBE AND PELVIC ABSCESS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	36	F.	....	43,000	....	Double pus tube; too weak to operate. December 15th.
				31,000	....	December 22d.
				45,900	....	December 29th; abscess burst per vaginam.
				20,200	....	January 4th, abscess opened in groin.
				15,200	....	" 8th.
				12,200	....	" 11th.
2	..	F.	5,400,000	34,000	....	Pelvic abscess.
3	38	F.	....	34,000	....	Pus tube. June 18th.
				34,600	....	June 19th.
				35,000	....	" 20th.
				40,000	....	" 27th, fever and vomiting just before catamenia.
				17,300	....	July 1st, temperature normal.
				11,500	....	" 8th, mass decreasing.
				12,000	....	" 14th, slight thickening still.
4	34	F.	4,202,000	32,500	60	Pus tube; septic arthritis; jaundice.
5	..	F.	4,880,000	30,000	....	Pus tube.
6	23	F.	....	29,200	....	Double pus tube.
7	29	F.	4,544,000	28,800	....	General purulent peritonitis.
8	20	F.	....	27,300		Pus tubes.
9	26	F.	3,800,000	27,000	65	Double pus tube. November 17th.
				25,000	....	November 19th, operated.
10	43	F.	5,210,000	26,600	....	Pus tubes.
11	28	F.	5,120,000	24,400	....	Pus tube.
12	..	F.	....	24,400	....	Pus tube four weeks' duration.
13	24	F.	5,876,000	24,000	....	Pus tube.
14	..	....	3,760,000	23,000	....	Pelvic abscess (fetid pus).
15	45	F.	....	22,000	....	Pus tube.
16	..	F.	5,200,000	22,000	....	Pus tube.
17	..	F.	5,200,000	22,000	....	Pus tube; operation; pus found.
18	35	F.	3,704,000	21,100	65	Pus tube operated.
19	19	F.	....	20,200	....	May 1st.
				23,800	....	" 11th, mass the same; pus tube.
20	26	F.	5,021.000	20,000	....	Pus tube.
21	..	F.	4,400,000	19,800	....	Pus tube.
22	21	F.	....	19,000	....	Pus tube. Temperature 99°. April 26th.
				21,100	....	No fever. May 2d.
				16,000	....	May 4th.
				18,600	....	" 9th.
				19,600	....	No fever.
				21,600	....	May 18th, flow of pus from os started by manipulation.
				18,200		
				16,300	....	Out doors.
23	54	F.	3,940,000	19,000	60	Pus tube and ovaritis; operation; pelvis full of foul pus; recovery after hysterectomy.
24	25	F.	3,860,000	18,800	....	Pus tubes.
25	?	F.	4,592,000	18.800	....	" tube.
26	18	F.	3,840,000	18,500	55	" tube; three hours after food.
27	32	F.	5,776,000	18,000	....	" tubes.
28	28	F.	5,000,000	18.000	....	" tube.
29	30	F.	3,410,000	18,000	....	" tube, etc.
30	21	F.	5,088,000	16,400	....	" tube; syphilis. October 7th.
			5,184,000	18,000	....	October 12th.
31	22	F.	4,300,000	16,000	80	Pus ear.
32	..	F.	3,800,000	16,000	....	Pus tube.
33	35	F.	....	15,600	....	Pus tube. May 8th.
				18,200	....	May 18th, transferred.
34	36	F.	4,656,000	15.600	60	Pus tube; large amount of pus found.
35	19	F.	....	15,300	....	Pelvic peritonitis.

another girl of three years whose temperature ranged between 101° and 104°, the leucocytes were only 7,224, or subnormal for that age (*vide infra*, page 336).

5. "Cases where at the primary operation the pus proved sterile show an increase in the leucocyte count when the wound becomes infected with pyogenic organisms" (as it always does).

6. "The red cells are rarely diminished, but the hæmoglobin is usually relatively low (mild secondary anæmia in these cases). This absence of a diminution in the red cells in these cases is the more remarkable because they were almost all in young children whose blood is much more sensitive to any deleterious influence than that of adults."

Qualitative Changes.

(*a*) As in other forms of tuberculosis there may be none at all. (*b*) The sluggish cell metamorphosis in purely tubercular cases is illustrated well by Case 17 of Dane's series, a boy of seven whose blood on the day of operation for hip disease with large abscess showed 8,932 leucocytes. The differential count was as follows:

	Per cent.
Polymorphonuclear neutrophiles	40
Small lymphocytes	49
Large lymphocytes and transitional forms	8
Eosinophiles	3

Eight ounces of pus were evacuated, in which cultures showed the absence of pyogenic organisms.

This case demonstrates that tubercular suppuration has no tendency to produce leucocytosis or to increase in the adult leucocytes (neutrophiles), but influences the blood only by producing what might be termed a functional debility of the blood through lack of nutritive substances in the plasma; the young cells do not grow up so fast as usual. This condition is by no means peculiar to tuberculosis, but occurs in a great variety of debilitated or cachectic conditions, as already stated.

(*c*) But when a septicæmia complicates the tuberculosis, cell metamorphosis appears to be accelerated, and we get with the

quantitative increase of leucocytes such qualitative changes as the following:

	Per cent.
Polymorphonuclear neutrophiles	84
Lymphocytes (small)	9
Lymphocytes (large and transitional)	6
Eosinophiles	1

This was a case (No. 33 of Dane's series) in which the abscess, sterile when first opened, had become inoculated with the staphylococcus aureus.

(*d*) Not every case with leucocytosis shows qualitative changes as the above. One of Dane's cases (No. 22, a boy of seven) showed a leucocytosis of 23,387, but only sixty per cent of these were polymorphonuclear, and two per cent eosinophiles.

In a case recorded by Dane (No. 32), *tubercular osteomyelitis* showed 6,083 white cells (subnormal, as the child was only two years old) with sixty-four per cent of polymorphonuclear cells. The pus from the bone cavity showed no pyogenic organisms on culture. Ordinary septic osteomyelitis gives very different results (see page 205). Dane's cases were almost exclusively hip and spinal affections.

The following cases from the Massachusetts Hospital records illustrate tuberculosis of other bones:

Case.	Diagnosis.	Red cells.	White cells.	Per cent hæmoglobin.
1	Tuberculosis of the knee joint	6,472,000	9,400	63
2	" " "	2,704,000	8,000	?
3	Metatarsal tuberculosis	4,650,000	6,500	61
4	Tubercular rib	5,016,000	5,800	73

III. ACUTE MILIARY TUBERCULOSIS.

Probably there are no important changes in the red cells or hæmoglobin. The number of cases on record is too small to enable me to speak positively on this point, but the acuteness of the disease would lead us to expect the normal or approximately normal conditions recorded in the few published cases.

About the leucocytes we know more.

Quantitative Changes.

Normal or subnormal counts are the rule. When occasionally there occurs a leucocytosis it may be inferred that the miliary process accompanies a suppurative one, and that the latter and not the former is responsible for the increased number.

Warthin[1] reports a case with autopsy in which he made over thirty counts of the white corpuscles, verifying the more remarkable results by repetition. Autopsy showed, besides miliary tuberculosis, a cavity in the lower lobe of the right lung and a suppurating focus about the seminal vesicles containing four ounces of pus rich in tubercle bacilli. Whether pyogenic organisms were also present is not stated. The leucocyte counts were as follows:

Day.	Hour.	Leucocytes.	Remarks.
December 6th	10 A.M.	3,500	
" 12th	8 A.M.	5,000	
" 18th	5 P.M.	3,500	
" 22d	10 A.M.	5,625	
" 22d	11:30 A.M.	4,725	
" 22d	3 P.M.	5,000	
" 22d	5 P.M.	3,125	
" 24th	8:30 A.M.	3,750	
" 24th	11:30 A.M.	3,750	
" 24th	2 P.M.	2,500	
" 24th	4:30 P.M.	2,500	
" 25th	8 A.M.	1,875	
" 28th	5:30 P.M.	3,750	Red cells, 4,125,000; hæmoglobin, 80 per cent.
" 29th	10 A.M.	1,250	
" 29th	2 P.M.	1,250	
" 29th	5:30 P.M.	3,750	
" 31st	12 M.	1,250	
" 31st	6 P.M.	2,500	
January 2d	11 A.M.	1,250	
" 2d	5 P.M.	2,500	
" 3d	2:30 P.M.	600	Severe chill. Count repeated several times.
" 5th	8:30 A.M.	3,750	
" 5th	11 A.M.	3,137	
" 5th	4 P.M.	8,125	Moribund.
" 6th	9 A.M.	10,000	
" 6th	10 A.M.	5,625	
" 6th	11 A.M.	2,500	
" 6th	12 M.	5,625	
" 6th	12:50 P.M.	Death.	

[1] Medical News, 1895.

In another case he found also a subnormal count. Rieder found normal counts in two cases. Von Limbeck states that the leucocytes are normal, but gives no counts.

The following cases from the Massachusetts Hospital records illustrate these points:

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	18	M.	....	3,600	....	Autopsy.
2	40	M.	....	3,750	....	"
3	14	F.	3,720,000	4,400	45	"
4	51	M.	4,664,000	4,800	....	" Phthisis (chronic) also.
5	12	F.	....	6,100	....	"
6	37	F.	....	7,800	....	" May 14th.
				7,200	....	" May 22d.
7	36	M.	....	7,600	....	" Phthisis (healed) also.
8	30	M.	....	9,257	....	" April 18th.
				9,457	....	" April 20th.
9	Adult.	M.	5,237,000	10,000	....	"
10	22	M.	....	12,700	....	" Phthisis with cavities also.
11	36	M.	....	23,000	....	" Hypertrophic cirrhosis also.

Qualitative Changes.

So far as I can ascertain Warthin's is the only record of the qualitative changes among the leucocytes. In the case above quoted, he repeatedly made differential counts of the leucocytes by Ehrlich's methods with this average result:

	Per cent.
Polymorphonuclear neutrophiles	91.49
Lymphocytes (small)	5.52
Lymphocytes (large and transitional)	3.09
Eosinophiles	0.
Myelocytes	.2

IV. TUBERCULOSIS OF SEROUS MEMBRANE.

1. Tubercular Peritonitis.

The blood condition is exactly as in other forms of tuberculosis, except in so far as it is modified by the drain exerted on the blood by diarrhœa or by transudation or exudation into the peritoneal cavity. Such events concentrate the blood by with-

drawing water and albumin from it and may give us a normal number of red cells per cubic millimetre, when in reality a considerable anæmia is present. As a rule, the blood shows a mild secondary anæmia without leucocytosis or with leucopenia. This is exemplified in the following tables from the Massachusetts Hospital records:

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	26	F.	3,120,000	2,240	58	
2	24	M.	5,360,000	3,800	....	January 6th, 1896.
			5,760,000	5,600	85	April 13th, 1896.
3	25	F.	....	3,900	....	Starting apparently from tubercular tube.
4	Adult.	M.	....	5,000	....	December 18th, 1895.
			4,560,000	8,250	76	January 10th, 1896.
5	30	F.	....	5,183	....	Starting apparently from tubercular tube.
6	20	F.	5,936,000	5,400		
7	44	M.	2,974,000	5,530	....	Pleuritic effusion also.
8	16	F.	3,840,000	6,000	56	
9	33	F.	4,000,000	6,000		
10	50	F.	5,240,000	6,400	....	Glandular tuberculosis also.
11	27	M.	....	6,700	....	May 22d, 1896.
				7,000	....	May 30th, 1896.
12	Adult.	M.	5,560,000	6,800		
13	44	F.	....	7,000	73	
14	17	M.	4,904,000	8,000	75	Tapped; one hundred and six ounces serous fluid obtained.
15	32	F.	....	8,200		
16	20	F.	4,200,000	8,500	58	Starting apparently from tubercular tube.
17	Adult.	F.	....	No increase		
18	50	F.	4,600,000	10,000	50	
19	Adult.	M.	5,200,000	10,000		
20	Adult.	F.	4,816,000	11,200		
21	21	F.	3,550,000	11,500	65	

I know of no differential counts of leucocytes in tubercular peritonitis. Presumably the sluggish metabolism of the cells found in other forms of pure tuberculosis exists here and causes an excess of the mononuclear (young) elements.

2. Tubercular Meningitis.

Remarkably few counts are on record so far as I can ascertain. Von Limbeck gives but a single case (with autopsy).

Four counts, the last on the day of death, showed the following:

May 22d, 1889:	Leucocytes	8,000
" 23d, 1889:	"	8,000
" 24th, 1889:	"	6,000
" 26th, 1889:	"	7,500

Rieder records two cases, in one of which the leucocytes were "normal or subnormal; in the other increased." In both diagnosis was confirmed by autopsy. The counts in these cases were as follows:

Case I.—February 26th, 1891:	Leucocytes	7,800
March 2d, 1891:	Leucocytes	5,900
Case II.—May 30th, 1891:	Leucocytes	14,400

Pick[1] saw two cases:

Case I.—February 28th, 1890:	Leucocytes	6,500
March 5th, 1890:	Leucocytes	8,000

In the second case there was also no leucocytosis. Autopsy in both. Sorensen's[1] two cases showed respectively 8,300 and 9,400 leucocytes. My own results in three cases are as follows:

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	24	F.	4,590,000	6,600	46	Autopsy.
2	45	M.	....	8,000	....	"
3	Adult.	M.	....	21,500	....	"

These are, so far as I can ascertain, the only cases of uncomplicated tubercular meningitis with autopsy in which blood examinations are recorded and in all but one of these nothing is said about red cells or hæmoglobin. Rotch mentions a single case complicated by an appendicitis in which the following count is recorded (girl of eleven years):

Red cells	5,298,750
White cells	37,500
Hæmoglobin (per cent)	68

Whether the leucocytosis was due wholly to the appendicitis or not we cannot tell.

[1] Cited by Rieder.

I have examined no other cases of uncomplicated tubercular meningitis in which autopsy confirmed the diagnosis. In two cases in which *clinically* the diagnosis was tubercular meningitis I found moderate leucocytosis, in one with ninety-one per cent polymorphonuclear cells. Two of the cases of miliary tuberculosis above mentioned had marked meningeal symptoms and plenty of tubercles in the meninges, but being a *general* and not a local process no conclusions as to the blood of tubercular meningitis can be drawn from the absence of leucocytosis in these cases.

On the whole, although it seems probable that pure tubercular meningitis, like other pure tubercular processes, has in most cases no tendency to raise the leucocyte count, the number of recorded cases is still too small to enable us to speak with certainty on the point. The red cells and hæmoglobin show probably the same changes as in other forms of tuberculosis.

3. Tubercular Pericarditis.

In one case in which tubercle bacilli were repeatedly demonstrated in the fluid obtained by tapping the pericardial sac I found no leucocytosis. I have not met with any other reports on the blood in this condition.

4. Tubercular Pleurisy.

No doubt a large proportion of all pleuritic effusions are tubercular in origin, but, so far as I have seen, no counts are recorded in cases proved by culture or inoculation to be tubercular. The low leucocyte counts in most pleurisies (see above, page 211) tend to show that they are tubercular and not due to pyogenic organisms.

Pick mentions that he finds no leucocytosis in tuberculous pleurisy when uncomplicated by phthisis, but reports no actual counts.

5. Glandular Tuberculosis.

In cases of so-called scrofulous glands, whether in children or adults, the blood shows no important changes except that in children the hæmoglobin may be considerably diminished.

Leucocytosis is absent unless an abscess has been opened and infected. Whether or not tuberculosis of the abdominal or other internal lymph glands affects the blood, I am unable to say.

6. Genito-Urinary Tuberculosis.

Here the opportunities for a secondary pyogenic infection are so good that in well-marked cases we find the blood of septicæmia present. The following cases, all involving the bladder, kidney, and the external genitals, illustrate this point:

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.
1	30	M.	3,796,000	14,452	44
2	41	F.	3,588,000	10,400	55
			3,000,000 +	14,452	
3	22	F.	....	10,200	

SYPHILIS.

Reiss, in an article in the *Archiv f. Dermatologie und Syphilis*, 1895, Heft 1, says that the general constitutional influence of the poison of syphilis is best indicated by the condition of the blood. In one hundred cases he has arrived at the following conclusions regarding the

Red Cells and Hæmoglobin.

During the time between the chancre and the secondary symptoms, the red cells are slightly decreased, but this is much more marked after the appearance of secondary symptoms and continues for a time even after treatment has begun. The hæmoglobin sinks steadily from the time of the primary lesion on, but is not especially affected by the eruption. Even under treatment the hæmoglobin *never* gets quite up to normal and prolonged mercurial treatment lowers it, although mercury has at first a beneficial effect on the hæmoglobin as well as on the other constituents of the blood.

Konried[1] goes further into detail. According to him, in the

[1] International Dermatological Congress, 1892.

first four to seven weeks after infection, the number of red cells remains normal, but the hæmoglobin begins to fall off, losing from ten to twenty per cent in that time. Afterwards it sinks steadily unitl treatment is begun, the number of corpuscles also falling slightly.

Newmann and Konried,[1] reporting in 1893 on two hundred cases, say that up to the time of the secondary symptoms from twenty-five to thirty per cent of hæmoglobin is generally lost, without much change in the red cells, which sink considerably in number after the outbreak of secondary lesions. Lezius[2] likewise finds no diminution in the *number* of red cells until the outbreak of secondary lesions.

All these changes, like those about to be described, are apt to be more marked in women than in men. In cases going on to the secondary stage untreated, the hæmoglobin may sink to as low as twenty-five per cent. In the tertiary stages and in hereditary and so-called "constitutional syphilis" the red corpuscles are much more seriously affected, diminishing considerably in number as well as in weight and color. The hereditary syphilis of infancy may indeed produce fatal anæmia and very low counts are common, with large numbers of nucleated red cells and great deformities in shape and size.

The effect of mercurial treatments on the red cells is interesting. Gaillard[3] found that the count of red cells increased during the first fourteen days and the hæmoglobin during the first twenty-four days of treatment. After that time, if mercury was still given, the hæmoglobin and later the number of corpuscles began to decline.

Konried (*loc. cit.*) found the hæmoglobin to rise during the administration of the first twenty-five to thirty-five inunctions, after which it began to go down. This was in cases in which treatment was begun just after the onset of secondary symptoms. In the worst cases it sank even as low as forty-five per cent despite treatment, and this usually means a bad prognosis and severe tertiary symptoms to come. In one of my own cases the hæmoglobin was only thirty-seven per cent, though the red cells were 4,988,000 (color index, .37).

[1] Wiener klin. Woch., 1893, No. 19. [2] Inaug. Dissert., Dorpat, 1889.
[3] Gaz. des Hôp., 1885, No. 74.

Cases often show spontaneous improvement in their anæmia as well as in other symptoms.

Justus[1] in three hundred cases claims to have observed a peculiar reaction of the hæmoglobin in syphilis, which does not occur in any other disease, and which he considers of much diagnostic value.

According to him, if in cases in which secondary symptoms have not yet appeared, we test the hæmoglobin and then give an inunction or a subcutaneous injection of mercury, we find that within twenty-four hours a very marked fall in hæmoglobin has taken place (ten to twenty per cent), owing to the action of the mercury on the weakened corpuscles. This sudden fall is followed by a gradual rise until within a few days the coloring matter is at a point slightly higher than before the mercury was given. In diseases other than syphilis this sudden drop does not occur. After the advent of secondary symptoms the peculiar reaction to mercury does not occur.

No evidence for or against this observation has as yet been brought forward by others. In view of the large number of cases in which Justus has tried the experiment it is certainly an interesting observation and deserves to be followed up. If true, it might give valuable assistance in the diagnosis of doubtful cases before the appearance of the "secondaries."

White Cells.

1. Here the changes are very characteristic. In the first stage the leucocytes are either normal or slightly increased, but the percentage of adult forms is almost always notably low, and that of the young forms (lymphocytes) high. If mercury is given at this stage, the adult forms begin to increase toward normal and the young forms proportionately to decrease. [Mercury given to healthy persons has just the opposite effect, increasing the young cells at the expense of the adult forms.] Iodide of potash works exactly like mercury in this respect, increasing the adult leucocytes in syphilis, while it diminishes them in healthy persons.

2. As the eruption breaks out leucocytosis (12,750 in one of my cases) generally appears, the relative proportions of young

[1] Verhandl. d. 5. Cong. d. Deut. dermatolog. Gesellschaft, September, 1895.

cells and of eosinophiles usually being increased. Treatment with mercury and potassium iodide tends to bring down the count of white cells, while it raises the count of red; and among the white cells to increase the adult forms.

In the *tertiary stages*, with the severe anæmia which is often present, there occur occasionally leucocytosis, not uncommonly with small percentages of myelocytes, and a marked lymphocytosis. Müller[1] has described four cases of anæmia in syphilis so severe as to simulate pernicious anæmia very closely. In one the red cells sank to 720,000. Laache[2] mentions a similar case.

There are no constant changes in the blood plates. Specific gravity follows pretty closely the hæmoglobin percentage.

Diagnostic Value.

Justus' reaction of syphilitic blood to mercury, if true, might be of great value in distinguishing early syphilis from various other causes of debility.

The occurrence in adults of leucocytosis with increased percentages of young leucoctyes and of eosinophiles, is very suggestive of syphilis as against tuberculosis, typhoid or malignant disease. In children, rickets and other diseases may give similar blood changes. The chief value of the blood examination, however, in syphilis is not for diagnosis but as a measure of the stage and severity of the infection. Low hæmoglobin and high percentages of the young forms of white cells are characteristic of severe types. Leucocytosis usually means that the case has got beyond the primary stage, while in the tertiary stage the presence of myelocytes with a marked anæmia is of serious import.

Certain cases of this last type may closely resemble pernicious anæmia, from which, however, they are to be distinguished by their low color index, the frequent presence of leucocytosis, and the relative infrequency of megaloblasts as compared with the normoblasts, in case nucleated red cells are present.

LEPROSY.

Winiarski (*Petersburger medicinische Wochenschrift*, 1892, page 365) gives a careful study of seventeen cases of leprosy.

[1] Charité-Annalen, vol. xiv. [2] *Loc. cit.*

He finds in young persons with mild cases no changes from the normal blood.

In severe cases, especially in old people, the anæmia may be severe (2,290,000 red cells with fifty-four per cent of hæmoglobin) and even comparable to pernicious anæmia (1,989,000 red cells with sixty-three per cent of hæmoglobin). In anæmic cases the color index is apt to be high, in one case 1.7(!). Such severe types are associated with an increase of the average diameter of the red cells which explains the high color index. The hæmoglobin was *not* relatively low in any case.

Leucocytes.

No increase was present in any case. Four cases were subnormal. The percentage of young cells, as in other debilitated conditions, is often high (forty-five to forty-seven per cent).

PART IV.

DISEASES OF SPECIAL ORGANS.

CHAPTER VII.

DISEASES OF THE DIGESTIVE APPARATUS.

1. Œsophagus (see Malignant Disease, page 287).
2. Stomach.

The conditions existing in the stomach may influence the blood profoundly in three ways:

(*a*) They may be such as to prevent the normal absorption of nitrogenous material on which the blood, like all tissues, is absolutely dependent. Then the blood becomes starved. The extreme of this condition is the so-called "atrophy of the gastric tubules" which may produce a fatal anæmia. In lesser degrees the same process is at work in many forms of chronic dyspepsia, gastritis, or chronic starvation.

(*b*) They may lead to severe and repeated hemorrhages.

(*c*) They may lead to an auto-intoxication which poisons the blood as well as other tissues.

On the other hand, it is probably through the influence of an altered blood serum on the duodenal mucous membranes that ulcer of the duodenum is a sequel to severe burns of the surface of the body.

For an account of the influence on the blood of digestion, ingestion of liquid, and starvation, see page 83.

DISEASES OF THE STOMACH

GASTRIC CANCER.

(See Malignant Disease, page 287.)

GASTRIC ULCER.

Red Cells and Hæmoglobin.

A severe anæmia is common. Out of the 28 cases in Table XXV., 13, or nearly one-half, had less than 50 per cent of hæmoglobin, and of the 21 in which the red cells were counted, 5 had under 3,000,000 red cells per cubic millimetre. The average count of red cells at the time when treatment began was 3,800,-000. There is no single disease, so far as I am aware, in which the red cells are so apt to be so low, except pernicious anæmia. Even cancer, as a rule, does not fall so low. This is due in part, no doubt, to the frequency of *hemorrhage* from the ulcer, but it is not uncommon to see very marked anæmia in patients who had never had a hemorrhage. The anæmia is as much cause as result of the ulcer; most probably both are due to a common (unknown) cause.

This anæmia is all the more striking when we remember that the frequent vomiting from which most patients suffer tends to concentrate the blood, *increase* the number of cells in a drop and so to make the blood seem less anæmic than it really is. This tendency to concentration is probably effective in the cases observed especially by Oppenheimer,[1] in which despite great pallor he found normal counts of red cells and hæmoglobin.

It is in such cases that the estimation of the dry residue of the blood serum would be of real value could it be made short and simple enough for clinical work. Grawitz, who is the prophet of this branch of blood examination, gives an interesting case illustrating this point.

A girl of twenty-five, suffering with peptic ulcer, and exceedingly pale, showed on counting the corpuscles 4,140,000 per cubic millimetre (no considerable reduction), and ninety per cent of hæmoglobin. A second count showed 4,840,000 corpuscles and ninety-one per cent of hæmoglobin. But the dry residue of the serum was reduced to three-fourths its normal amount. The serum suffers in anæmia as much as the corpuscles do. Any influence which deprived the serum of one-fourth of its normal solids (œdema being absent) must have really affected the corpuscles very much. Therefore the corpuscles must actually have been reduced to about 3,800,000, the reduction being masked by the concentration of the blood from vomiting. Lymph cannot have run into the vessels and diluted the serum, for (owing to the vomiting) the tide is all the other way. If then the serum is

[1] Deut. med. Woch., 1889, No. 42.

reduced a quarter the corpuscles must be so likewise. Unfortunately, to test the dry residue of the blood serum requires more time, skill, and apparatus than clinicians are apt to have. It is valuable whenever we wish to know whether or not an anæmia is being masked by concentration of the blood.

In severe cases the usual *qualitative evidences* of secondary anæmia (deformities, nucleated corpuscles) are to be found.

TABLE XXV.—GASTRIC ULCER.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	28	F.	....	20,000	80	March 27th. Temperature up; no cause known.
					95	April 15th.
2	52	M.	2,031,200	17,200	30	Hemorrhage and perforation.
3	......	F.	5,024,000	12,500	82	
4	20	F.	....	....	77	April 23d.
					88	" 30th.
					90	May 5th.
			7,700,000	10,000	....	" 14th. Vomiting.
					65	" 27th.
5	23	F.	3,210,000	9,280	25	January 16th.
			4,000,000	7,000	35	February 1st.
					40	" 8th.
					55	" 17th.
6	22	F.	4,280,000	8,800	51	August 26th, 7 P.M. Gastric ulcer and chlorosis.
					52	September 2d.
					61	" 9th.
					72	" 15th.
7	20	F.	5,136,000	8,800	62	
8	55	F.	2,580,000	8,666	40	
			2,100,000	6,000	25	One week after, on enemata.
			3,100,000	5,332	46	One month later.
			3,620,000	7,500	....	Ten days later.
9	67	M.	3,488,000	7,000	42	August 13th. Hemorrhage one-half pint four days ago and same to-day.
			2,896,000	9,000	37	August 24th.
10	23	F.	1,672,000	6,000	40	Hemorrhage one pint the previous day; blood in stools.
11	......	F.	2,024,000	5,750	25	Slight deformities in red cells. December 6th.
			2,464,000	4,000	30	Slight deformities. December 13th.
			3,056,000	15,500 (Digestion.)	36	No deformities. December 21st.
			3,450,000	8,000	48	
12	29	M.	1,672,000	5,700	20	June 4th. No blood.
			1,560,000	1,800	15	" 18th. Doing well; slight blood in vomitus, none in stools.
			3,048,000	8,000	33	July 3d.
			3,344,000	3,600	58	" 17th.

TABLE XXV.—GASTRIC ULCER (*Continued*).

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
13	23	F.	5,240,000	5,600	54	February 14th.
			5,144,000	....	55	March 2d.
					48	" 6th.
14	......	F.	3,460,000	5,500	43	Poikilocytosis.
15	Adult	F.	5,168,000	4,600	78	
16	22	F.	3,584,000	4,400	85	
17	24	F.	3,200,000	4,000	45	
					37	Two weeks later.
					45	Three " "
					55	Five " "
					65	Six " "
18	22	F.	4,704,000	4,000	65	
19	22	F.	5,152,000	2,800	46	
20	27	F.	5,776,000	2,600	95	
21	..	...	1,808,250			
22	23	F.	....	....	35	
23	37	F.	....	....	73	September 6th.
					75	" 18th.
24	21	F.	....	....	108	
25	24	F.			52	October 10th.
			....	....	80	" 15th.
26	22	F.	....	....	48	
27	......	...	....	....	55	March 12th.
					65	" 24th.
					70	April 1st.
28	17	F.	....	....	50	May 7th.
					55	" 16th.
					70	" 24th.
					70	April 1st.
					80	" 8th.

Hæmoglobin.

As a rule the color index is low. Only one examination in the cases of the Massachusetts Hospital series showed an increased amount of hæmoglobin per corpuscle, and as this was not repeated or verified, it may have been a mistake. In all the other thirty examinations the color index was low (*e.g.*, Case 5, color index = .39).

Yet Osterspey records 1,900,000 red cells with 31 per cent of hæmoglobin (color index = .81); 3,296,000 with 70 per cent hæmoglobin (color index = 1.09); 4,048,000 with 84 per cent hæmoglobin (color index = 1.05). Such cases are certainly rare.

White Cells.

Leucocytosis is practically never seen except after hemorrhage and during digestion. When patients who have been fed for some time by the rectum are first given food by the mouth, the digestion leucocytosis may be very great, as in Case 11 of the above series, in which the cells increased from 4,000 to 15,500! The presence of a leucocytosis, when the influence of bleeding and digestion are excluded, is against the diagnosis of ulcer of the stomach.

DUODENAL ULCER.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	30	M.	3,776,000	Normal	50	
2	47	M.	2,100,000	12,000	35	July 24th, much coffee grounds.
				7,650	....	July 29th (five days fasting).
				11,600	....	Four hours after meals.
				11,000	....	Constant feeding, July 30th.
			2,480,000	6,000	38	August 8th.
			2,630,000	6,500	36	August 21st, operation.

These figures are given simply to show that the blood in duodenal ulcer undergoes much the same changes as in gastric ulcer, and need no further comment.

ACUTE GASTRITIS AND DYSPEPSIA.

Acute gastritis or gastro-enteric attacks (Hayem's "*embarras gastrique*") do not affect the red cells or hæmoglobin, but are very often accompanied by leucocytosis (see Tables XXVI., A and B). Where this is the case, it may help us to exclude typhoid fever, which has no leucocytosis. Even a twenty-four hours' dyspeptic attack may increase the leucocytes notably, as in Cases 1 and 2 in Table XXVI., A, and the presence of such an increase need not make us suspect anything behind the dyspepsia. It is probably to be classed as a toxic leucocytosis due to absorption of morbid products from stomach or intestine. Fibrin may be increased during the period of leucocytosis.

TABLE XXVI., A—ACUTE GASTRO-ENTERITIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	31	M.	7,000,000	18,000	....	Well next day. Temp. 104°.
2	18	F.	5,184,000	15,000	85	Well next day.
3	30	F.	4,860,000	14,200	80	Well in three days.
4	23	F.	6,244,000	11,600	86	Well in two days.
5	17	F.	4,600,000	11,000	70	
6	33	M.	....	marked increase	....	Well next day.
7	70	F.	4,632,000	10,000	90	
8	37	M.	4,186,000	9,200	68	
9	57	F.	....	6,000	....	Temperature 101°.
10	23	F.	5,144,000	5,400	95	

TABLE XXVI., B—DYSPEPSIA AND GASTRITIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	24	M.	6,280,000	22,700	....	Gastralgia; constipation; whole belly tender.
				12,800	.. ..	Three days later; well in a week.
2	27	F.	4,750,000	14,000	74	At mealtime, 11,200; four hours later, 12,150.
3	26	F.	4,920,000	11,000	55	Dyspepsia.
4	23	M.	....	11,000	....	Acute gastritis.
5	....	...	5,016,000	8,924	86	
6	37	M.	....	7,326	77	Chronic gastric catarrh.
7	30	F.	3,678,000	7,000	75	Nervous dyspepsia.
8	41	M.	4,524,000	6,000	68	Before meal, November 1st, 6,000; November 2d, 6,300. After meal, November 1st, 6,800; November 2d, 7,400.
9	49	F.	4,200,000	4,000	80	Chronic gastritis.
10	18	F.	5,016,000	3,200	45	Dyspepsia.
11	60	M.	3,504,000	2,800	50	Chronic gastritis.

CHRONIC GASTRITIS.

(See Cases 6, 9, and 11, Table XXVI., B.)

Here the conditions are different and we never find an increase of the white cells, but often a decrease due to malnutrition. Digestion may produce no leucocytosis, or the increase may be very slight and late in appearing (four to five hours after a meal instead of two to three hours).

Anæmia is very often present and may be extreme. It is believed by very high authorities that a *pernicious* anæmia may be caused by chronic gastritis with atrophy of the gastric tubules. The writer has never had the good fortune to see such cases.

The practical points about the blood of chronic gastritis are:

(*a*) The not infrequently severe anæmia.

(*b*) The not infrequent absence of digestion leucocytosis as in gastric cancer, from which therefore the *absence* of digestion leucocytosis does not distinguish it.

The presence of a leucocytosis militates against the diagnosis of chronic gastric catarrh, and, if hemorrhage is excluded, points toward cancer.

HYPERACIDITY AND HYPERSECRETION.

The leucocytes average higher in these conditions than in chronic gastritis or dyspepsia with normal or decreased secretions (see Table XXVII.). Otherwise the blood is not remarkable.

TABLE XXVII.—HYPERACIDITY AND HYPERSECRETION.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	Adult.	M.	5,024,000	12,300	82	
2	30	F.	5,768,000	10,800	82	Chronic gastritis.
3	40	M.	5,300,000	10,000	85	Slight digestion leucocytosis: 12,270 before meal, 14,300 three hours later.
4	40	M.	3,340,000	7,780	7	Dilated stomach; no digestion leucocytosis.
5	28	F.	4,016,000	5,994	76	
6	57	M.	4,160,000	3,600	34	Lead poisoning and dilated stomach.

DILATED STOMACH.

No.	Age.	Sex.	Red cells.	White cells.	Per cent. hæmoglobin.	Remarks.
1	22	F.	6,216,000	10,400	83	
2	51	M.	4,184,000	9,600	55	
3	47	M.	4,720,000	8,000	....	Nervous dyspepsia.
4	30	F.	5,000,000	6,000	75	Movable kidney.
5	64	M.	5,264,000	4,600	70	

DILATED STOMACH.

In many cases proteid absorption is so faulty that the blood is severely starved, but the *anæmia* may be concealed by the *concentration* of the blood brought about by the constant vomiting of large amounts of fluid. Kussmaul has shown that patients *often vomit more fluid than they ingest,* and it is obvious what must be the drain of this process on the fluids of the blood and all other tissues.

Digestion leucocytosis is often absent, as in cancer or chronic gastritis.

CORROSIVE GASTRITIS.

The blood was examined in a case of this kind in 1895 at the Massachusetts General Hospital with the following result: Red cells, 3,792,000; white cells, 32,500; hæmoglobin, fifty-three per cent.

DISEASES OF THE INTESTINE.

INFLUENCE OF SALINE CATHARTICS ON THE BLOOD.

Hay[1] gives the following figures, showing the effect of sulphate of sodium in concentrating the blood: Healthy man of thirty-three, 3:35 P.M. Red corpuscles, 5,025,000; given 85 c.c. of a concentrated solution of sulphate of sodium in water; thirty-five minutes later blood count showed red corpuscles, 6,540,000; sixty-five minutes later blood count showed red corpuscles, 6,790,000; four hours later blood count showed red corpuscles, 4,930,000. Evidently much fluid was drawn out of the blood-vessels and then within four hours the tissues had supplied the loss and the blood had returned to its normal density.

Hay also showed that dilute solutions of the same salt had far less effect in concentrating the blood. Farther he demonstrated that if the blood is *already concentrated* when the saline is given, no purgative effect follows.

Grawitz confirms these results; he found also that common salt still further concentrates the blood (hence its production of

[1] Hay: "The Action of Saline Cathartics." Journal of Anatomy and Physiology, 1882, p. 430.

thirst), and considers that (as this concentration accelerates *coagulation*) the household use of salt water as a remedy to stop hemorrhage is well founded.

TABLE XXVIII.—ENTERITIS, COLITIS, AND DYSENTERY.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	45	M.	3,840,000	17,000	50	Chronic dysentery. August 26th.
				14,300	....	September 3d.
				7,700	....	" 5th, dysentery ceased.
				8,800	....	" 20th.
2	25	F.	....	17,000	....	Chronic entero-colitis.
3	Adult.	M.	3,624,000	13,000	58	Chronic entero-colitis.
4	Adult.	M.	4,320,000	12,400	....	Ulcerative colitis.
			2,732,000	10,600	....	Two weeks later.
			4,488,000	6,000	....	Three weeks later; much improved.
5	39	F.	6,776,000	8,900	100	Acute febrile dysentery; bloody movements every hour.
6	8	F.	4,800,000	7,900	....	Ulcerative colitis.
7	Adult.	M	4,100,000	7,560	72	Chronic enteritis.
8	27	M.	4,872,000	7,000	....	" diarrhœa and tetany.
9	20	M.	5,008,000	6.460	39	" diarrhœa (tubercular?).
10	26	M.	4,900,000	5,300	80	Bloody stools ten days.
11	65	M.	....	5,200	80	Catarrhal entero-colitis.
12	40	F.	2,996,000	5,000	37	Chronic colitis.
13	27	F.	4,500,000	5,000	70	Diarrhœa.
14	34	F.	3,920,000	4,200	71	Chronic colitis.

ACUTE ENTERITIS.

Practically the great majority of cases of acute enteritis are part of a gastro-enteric attack, and in Table XXVI. (see page 241) the two have been lumped together. What was said of that table (page 240) need not be here repeated. Besides the slight leucocytosis there mentioned, we may find in cases in which the stools are very watery, a temporary concentration of the blood with increased specific gravity and red corpuscles.

CHRONIC DIARRHŒA.

(See Table XXVIII.)

In acute diarrhœa the other tissues respond to meet the loss of fluid sustained by the blood, and the blood is soon normal again. But when this process goes on long, the body becomes

so wasted that the blood must share in the starvation and the albuminoids are drained out of it, leaving it watery and poor in corpuscles. A patient of Grawitz after years of chronic dysentery had but 1,880,000 red cells per cubic millimetre, while the serum had twice the normal amount of water and half the normal amount of solids.

Cases 1, 3, 4, 12, and 14 of the series in Table XXVIII. show similar conditions. The hæmoglobin, however, usually suffers most and the color index is low.

Leucocytosis is rare, but does occasionally occur, possibly owing to some complication.

TABLE XXIX.—INTESTINAL OBSTRUCTION.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	....	...	3,120,000	20,800	....	Cancer.
2	52	M.	5,568,000	18,860	....	9th of May, cancer.
				18,800	....	17th of May, cancer.
3	Adult.	M.	....	14,666	....	No fæces three days. No urine two days.
				12,400	....	One day later, no fæces; urine drawn by catheter.
				4,100	....	Three days later, bowels moved six times.
4	35	M.	3,504,000	12,000	....	Chronic obstruction with hemorrhage.
5	21	M.	5,150,000	12,000	....	Obstruction (by a band).
6	56	F.	4,440,000	12,000	52	Cancer.
7	57	F.	4,272,000	11,000	75	Cancer.
8	Adult.	M.	5,800,000	6,800		
9	72	M.	4,850,000	6,000		
10	Adult.	M.	5,200,000	4,000		
11	"	M.	5,540,000	4,000		

Cholera is discussed on page 184.
For *appendicitis* see Abscess, page 195.

INTESTINAL OBSTRUCTION.

The only point brought out by Table XXIX. is that the white cells may be increased, especially where the obstruction is cancerous. Hence the blood count cannot be relied on to help us in the diagnosis between obstruction and peritonitis. It is more likely that the examination of the amount of fibrin will be

useful, as it is said to be increased in peritonitis and not in obstruction.

DISEASES OF THE LIVER.

CATARRHAL JAUNDICE.

The serum is colored yellow or greenish-yellow and contains bile pigments in solution. In mild cases, *i.e.*, where some bile goes to the intestine and the obstruction is not long standing, *the blood is practically normal*, as the cases in Table XXX show.

TABLE XXX.—CATARRHAL JAUNDICE.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	25	F.	4,310,000	10,000	77	Acute gastritis.
2	....	...	....	10,000	90	
				8,000	....	Three days later.
3	42	M.	2,896,000	8,775	47	Alcoholic gastritis.
4	21	M.	4,800,000	7,500	65	
5	53	M.	4,240,000	6,793	79	
6	29	M.	....	6,200	82	Dilated stomach; lead poisoning.
7	....	M.	4,996,000	6,000	78	
8	35	M.	4,350,000	4,900	85	Chronic.

No one of the eight cases shows any leucocytosis and the red cells and hæmoglobin have not suffered except in the alcoholic case in which other causes for anæmia were present. This is contrary to the observations of Grawitz, who found constantly leucocytosis, but agrees with those of v. Limbeck and Hayem, who never found any increase of leucocytes or any other changes in the blood count. Coagulation and the amount of fibrin are normal. Von Limbeck noticed an *increased resistance* of the red cells to the influence of distilled water and dilute saline solutions which in normal blood dissolve the hæmoglobin. He noticed also that the *size* of the red corpuscles was *greater than normal*, their volume in a given amount of blood being seventy-seven to eighty-one per cent (*i.e.*, they take up seventy-seven to eighty-one per cent of the room occupied by the drop) while the normal is about forty-four per cent. This was in cases with only from 4,000,000 to 5,200,000 red cells per cubic millimetre, so that it was evidently due not to an overcrowding of the drop

with red cells but to a true increase of size in the individual cells. The same fact has been attested from a different point of view by the investigations of v. Noorden, who found the solid residue increased, and of Hammerschlag; and Grawitz has noted an increase in the specific gravity of the whole blood, though that of the serum remained normal.

Qualitative Changes.

Grawitz noted in severe cases that crenation took place much more rapidly than usual in freshly drawn blood, and that the rouleaux formation did not take place. This latter point was also noticed by Hofmeier[1] in icterus of the new-born. Silbermann[2] noticed in the same disease great deformities in the size and shape of the cells. In severe febrile icterus Weintraud noted in the red cells the white spots and streaks with active (molecular) movements described by Maragliano (see page 71) as endoglobular degenerative changes.

Summary.

Normal blood, except for increased size of the red cells and some degenerative changes in severe cases.

Diagnostic Value.

The constant presence of leucocytosis excludes an uncomplicated "catarrhal" jaundice, and points to the probability of malignant disease or inflammation (cholangitis, abscess). Syphilis and cirrhosis of the liver might show the same condition of the blood unless the characteristics of syphilitic blood were very marked (see page 234). From a severe cholæmia the absence of any marked anæmia distinguishes a purely catarrhal case. (For the changes in cholæmia see page 252.)

CIRRHOSIS OF THE LIVER.

1. Ordinary (Atrophic) Cirrhosis Without Jaundice.

In the early stages (according to Hayem) neither the red cells nor the hæmoglobin fall considerably. Most other observers

[1] "Die Gelbsucht der Neugeborenen," Stuttgart, 1882.

[2] "Die Gelbsucht der Neugeborenen." Arch. f. Kinderheilk., 1887, p. 401.

(perhaps thinking chiefly of the later stages) report marked anæmia. Wlajew[1] counted from 3,000,000 to 4,000,000 red cells; v. Limbeck had a case with only 1,500,000. He noted that the count might be increased after a tapping in cases with ascites, owing to the concentration of the blood from the rapid refilling of the belly with serum. Grawitz, on the other hand, noticed precisely the opposite effect in a case whose blood before tapping had been concentrated by cyanosis, the heart's action being embarrassed by the ascites. After tapping, when the heart's action had become easier and stronger, the cyanosis disappeared and the blood count fell from 4,700,000 to 4,300,000. In v. Limbeck's case it rose from 4,680,000 to 5,160,000. The moral is that we should draw no inferences from the count of red cells soon after a tapping.

The ten cases in Table XXXI., A, were all advanced and their red cells averaged only 3,580,000 + per cubic millimetre. They steadily decrease as the disease progresses, one case getting as low as 1,300,000; but the anæmia may be concealed by cyanosis and concentration.

Qualitative Changes.

Hayem noticed a curious stickiness of the red corpuscles, a great tendency to adhere to each other. Von Limbeck looked for it, but could never find it. Hayem and Maragliano noticed degenerative endoglobular changes in the red cells (“*état cribriforme*”).

Hæmoglobin.

Usually the color index is low; the average was .66 in the ten Massachusetts Hospital cases.

White Cells.

Except after recent hemorrhage none of our cases showed any leucocytosis, and the average count was 7,240, some cases having notably low figures (2,400, 3,000, 4,500).

Hayem's results agree with this. Von Limbeck makes no definite statement on this point. Rosenstein and Wlajew found leucocytosis, the latter 12,000 to 17,000. Possibly their cases include the forms of cirrhosis *with* jaundice in which (see Table XXXI., B) the white cells are more often increased.

[1] Ref. in Petersburger med. Woch., 1894, No. 43.

The forms of hypertrophic cirrhosis *without* jaundice (fatty infiltrated liver) are here classed with the atrophic cases whose blood has just been described.

TABLE XXXI., A.—CIRRHOTIC LIVER WITHOUT JAUNDICE.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo-globin.	Remarks.
1	53	F.	2,950,000	16,000	....	Recent hemorrhage.
2	41	M.	4,300,000	12,750	55	Liver enlarged ; ascites.
3	48	M.	4,992,000	9,088	62	Recent hemorrhage.
4	53	M.	2,120,000	9,000	23	March 15th.
			1,300,000	7,500	22	April 8th.
					15	April 18th.
					15	April 29th.
			2,350,000	6,000	20	May 10th.
			2,375,200	5,300	26	May 11th.
			2,450,000	5,200	30	June 10th.
			4,500,000	7,800	25	June 16th.
5	36	M.	3,440,000	8,320	46	Liver enlarged.
6	54	M.	4,680,000	5,000	48	Liver, atrophic. July 12th.
			4,312,000	4,000	62	July 25th.
7	?	M.	2,920,000	4,500	56	Liver atrophic. October 30th.
				13,400	....	November 7th, during digestion.
				15,300	....	" 11th, during digestion.
8	63	M.	3,844,000	3,000		
				6,170	....	Erysipelas. Died.
9	50	M.	3,568,000	2,400	50	Liver atrophic.
10	52	M.	3,440,000	2,400	50	August 6th. Died September 2d.

TABLE XXXI., B.—CIRRHOTIC LIVER WITH JAUNDICE.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo-globin.	Remarks.
1	38	M.	3,400,000	19,500	50	
2	45	M.	4,568,000	14,000	65	Liver enlarged.
3	35	M.	5,016,000	12,000	....	Liver enlarged.
4	57	F.	....	....	....	Adult cells, 83 per cent; young cells, 17 per cent.
5	36	M.	2,064,000	4,300	50	Jaundice only transient.
6	50	M.	2,904,000	2,400	54	Autopsy (hypertrophic cirrhosis).

2. HYPERTROPHIC CIRRHOSIS WITH JAUNDICE.

Red Cells.

True (biliary) hypertrophic cirrhosis *with* jaundice has according to Hayem an intense anæmia in many cases. In others

it has no more effect on the blood than ordinary atrophic cirrhosis. The six cases in Table XXXI., B, averaged a little lower in the count of white cells than the ten atrophic cases, 3,200,000 as contrasted with 3,580,000.

Hæmoglobin.

In a single case of this variety of cirrhosis Hayem found in four successive blood examinations a color index of more than 1. His counts are as follows:

Date.	Red cells.	White cells.	Per cent hæmoglobin.	Color index.
January 9th.........	1,599,600	....	41	1.27
" 11th.........	1,884,000	21,803	50	1.39
" 12th.........	1,798,000	18,082	50	1.46
" 15th.........	1,971,000	15,500	53	1.40

Dried specimens showed an increased average diameter of the cells as in pernicious anæmia. The patient died January 15th and the autopsy confirmed the diagnosis of hypertrophic cirrhosis.

The observations of v. Limbeck of the increased volume of the red cells in *jaundice* may perhaps be another example of the condition here noted by Hayem. The presence of bile in the blood makes all hæmoglobin estimations unsatisfactory.

Only one of our six cases showed this same condition—Case 5 in Table XXXI., B. The corpuscles numbered 2,064,000, or forty per cent, and the hæmoglobin fifty per cent, a color index of 1.25. This case was jaundiced at the time of the examination.

I have seen no confirmation of Hayem's observation by any other writer.

White Cells.

Leucocytosis is commoner in this than in the other variety of cirrhosis. Hanot and Mennier found from 9,000 to 21,800 leucocytes per cubic millimetre in five cases of hypertrophic cirrhosis and an average of 6,600 in ordinary cirrhosis. Leucocytosis was present in four of the six cases of the Massachusetts Hospital series, the average of all six being 9,000.

Diagnostic Value.

The blood of either form of cirrhosis has no diagnostic value, so far as I know, except to exclude abscess and hydatids. If no leucocytosis is present, abscess and hydatid cyst can usually be excluded.

HYDATID CYST OF THE LIVER.

The only observations which I have met with are those of Hayem, who states that the blood shows leucocytosis and increased fibrin.

ACUTE YELLOW ATROPHY OF THE LIVER.

Grawitz records a case with 5,150,000 red cells and 16,000 white cells.

A single case with autopsy was studied at the Massachusetts General Hospital in 1894, the blood showing 5,520,000 red cells, 12,000 white cells, and sixty per cent of hæmoglobin.

PHOSPHORUS POISONING.

Taussig,[1] v. Jaksch,[2] Badt,[3] and v. Limbeck[4] note an *increase* in the normal number of red cells per cubic millimetre. Taussig found 8,650,000 per cubic millimetre; Badt, 6,400,000, 6,500,000, and 6,800,000 in three successive cases; v. Limbeck, 6,500,000 and 7,900,000. That this increase is not due to concentration of the blood through vomiting of liquid is proved by v. Limbeck's last case, in which no vomiting whatever took place.

The count usually falls to normal within a few days. All these changes were verified in thirty-three cases at the Stockholm Hospital in 1892 (see Stockholm Hospital reports for 1892).

The white cells in v. Limbeck's second case were increased to 12,500. In v. Jaksch's five cases the counts were 58,750, 48,000, 8,000, 4,070, and 3,400.

[1] Arch. f. experiment. Path. und Pharm., vol. xxx.
[2] Deut. med. Woch., 1893, p. 10.
[3] Dissert., Berlin, 1891.
[4] *Loc. cit.*, p. 84.

CHOLÆMIA.

When jaundice is intense and long standing, as in complete obstruction of the bile ducts by gall-stones or tumors, the blood is weakened very notably, and hæmoglobin and the count of corpuscles fall steadily. Very little is to be learned upon the subject from the literature, but the qualitative changes mentioned under catarrhal jaundice are much more marked, and leucocytosis is apt to be present.

TABLE XXXII., A.—GALL-STONES.

No.	Age.	Sex.	Red cells.	White cells.	Remarks.
1	39	F.	4,768,000	24,400	Gall-stone and cholangitis. Operated.
2	30	F.	4,820,000	20,000	Slight cholangitis. Autopsy.
3	63	F.	4,610,000	18,800	
4	40	F.	4,520,000	13,000	No pain; simple jaundice.
5	40	M.	....	10,256	Enlarged gall-bladder.
6	25	F.	5,072,000	8,800	Jaundice. No fever.
7	22	M.	3,288,000	8,000	Jaundice.
8	25	F.	4,900,000	8,000	
9	25	F.	2,844,000	7,400	
10	37	F.	....	7,300	October 1st.
				8,200	" 5th.
11	24	M.	4,320,000	4,000	Jaundice and pain recurrent.

TABLE XXXII., B.—CHOLANGITIS.

No.	Age.	Sex.	Red cells.	White cells.	Remarks.
1	....	F.	4,800,000	50,000	Suppurative cholangitis.
2	....	F.	6,400,000	30,000	
3	....	F.	4,960,000	22,000	
4	21	M.	4,976,000	14,800	Jaundice and cholæmia.
5	65	M.	....	14,186	Gall-stones; chills.
6	....	....	....	11,000	October 20th. Operation October 22d. Abscess of liver.
7	28	M.	6,640,000	9,000	Catarrhal.
			5,592,000	6,800	
8	34	F.	4,770,000	4,400	Catarrhal.

GALL-STONES.

Netter[1] and Sittmann[2] have found pyogenic organisms in cultures from the blood of patients with gall-stones, as have also Gilbert and Girode.[3]

[1] Progrès Médical, 1886, No. 46.

[2] Deut. Arch. f. klin. Med., 1894, p. 323

[3] La Semaine Méd., 1890, No. 58.

Of the 11 cases of this disease examined at the Massachusetts General Hospital 2 were complicated with cholangitis (see Table XXXII., A). Excluding these 2, leucocytosis was present in only 2 of 9 cases. The red cells were low in 2 cases (2,800,000 and 3,900,000).

The absence of leucocytosis helps us to distinguish the disease from peritonitis and appendicitis, and excludes suppurative cholangitis.

CHOLANGITIS.

Here the leucocytosis is well marked whenever the inflammation has got beyond the catarrhal stage (see Table XXXII., B) and helps us to exclude simple impacted gall-stone, with or without colic. Cancer may or may not produce leucocytosis, but does not usually increase the fibrin network; it is said by Hayem that cholangitis does increase it.

ABSCESS OF THE LIVER.

In all but one of the cases seen by the writer (see Table XXXIII.) the leucocytosis has been very marked. I have never been able to account for its absence in that case.

The blood does not differ from that of cholangitis with suppuration. From cancer it may often be distinguished by the absence of increased fibrin network in cancer, while it is always increased in suppurations.

TABLE XXXIII.—ABSCESS OF THE LIVER.

No.	Age.	Sex.	Red cells.	White cells.	Remarks.
1	20	M.	4,533,000	33,200	January 11th, 1894.
			5,000,000	48,000	" 14th. Operated.
2	15	F.	3,750,000	26,800	Operated.
3	60	F.	4,460,000	18,000	Operated.
4	....	M.	....	12,600	
5	51	F.	3,440,000	9,600	

CANCER OF THE LIVER.

(See Malignant Disease, page 301.)

GUMMA OF THE LIVER.

Von Jaksch in a single case found red cells, 2,756,000; white cells, 6,100.

DISEASES AFFECTING THE HEART.

PERICARDITIS.

(See Inflammation of Serous Membranes, page 215.)

ENDOCARDITIS.

In many cases of acute endocarditis the blood shows no changes. In others, whatever alterations there may be are covered up by those involved in the *rheumatic* arthritis associated with the endocarditis.

In certain cases, however, particularly in *ulcerative or malignant endocarditis,* we may find the signs of a pyogenic infection (see page 188). Sometimes pyogenic cocci can be cultivated from the blood and if present *may be of the greatest value in a diagnosis* always difficult to make.

Grawitz goes so far as to say that in doubtful cases repeated negative results of cultures from the blood make it unlikely that ulcerative endocarditis is present.

Sittmann[1] considers that important help may be given as to the position of the primary focus of infection by the nature of the organism present in blood cultures—*i.e.*, the pneumococcus pointing to the lung, the colon bacillus to the intestine, etc.

Red Cells.

As in all forms of septicæmia marked anæmia rapidly develops, more rapidly probably than in any other disease. The hæmoglobin loses about equally with the corpuscles, according to most observers—that is, the blood destruction is so rapid that the red cells do *not* get thin before they die, as is usually the case, but are cut off in the prime of health.

Further evidence of rapid blood destruction is seen in the hæmoglobinæmia often present.

[1] *Loc. cit.*

Roscher (*loc. cit.*) records counts of 4,400,000 and 2,750,000, both fatal cases. In one case seen by the writer the count was 3,792,000 with fifty-eight per cent of hæmoglobin.

White Corpuscles.

Rieder reports a single case showing these variations:

	Temperature.	White cells.
January 2d, 1891	105°	17,000
" 3d, 1891	99°	13,700
" 8th, 1891	103°	15,500
" 10th, 1891	101.5°	18,000
" 12th, 1891	101.5°	21,300
" 18th, 1891	101°	18,800
" 22d, 1891	104.5°	13,000

February 11th, patient died.

Pée found leucocytosis. Roscher in two cases found: Case I.: 8,800 leucocytes; patient died in two days. Case II.: 16,800 and 12,000. Krebs in one case found: October 27th, 15,500; October 28th, 44,200; the patient died same day.

Five cases were counted at the Massachusetts Hospital with the following results. In one only the fresh blood was examined and showed marked leucocytosis; in the others:

Case.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	....	30,100	....	May 27th.
		15,800	....	May 30th.
		18,100	....	June 17th.
2	....	25,700	....	May 22d.
		27,840	....	May 24th.
		18,100	....	May 26th.
		22,000	....	May 28th.
3	....	12,600	....	January 13th.
		14,500	....	January 14th.
		20,400	....	January 16th.
		24,000	....	January 18th; died.
4	3,792,000	10,000	58	

I have no cases of acute benign endocarditis to compare with this, so that I do not know whether leucocytosis would be equally marked there.

Diagnostic Value.

(*a*) Blood cultures should never be omitted in cases of suspected malignant endocarditis. When positive they are of

great value. (*b*) In excluding typhoid the presence of leucocytosis is important.

MYOCARDITIS.

Whenever stasis and disturbance of the circulation result from weakness of the heart wall, blood changes identical with those described under Valvular Heart Disease are present. Otherwise the blood is normal.

VALVULAR HEART DISEASE.

Grawitz divides valvular heart disease into three stages with corresponding blood conditions:

1. Stage of full compensation: blood normal.
2. Stage of *acute* failure of compensation: blood diluted (Oertel's "plethora serosa").
3. Stage of chronic stasis and cyanosis: blood concentrated for the most part; at times diluted as well.

1. A valvular lesion *per se* has no effect on the blood.

2. When compensation fails and blood pressure is lowered, we find (*especially in the venous blood*) that the fluid from the surrounding lymph spaces has made its way into the vessels and dilated the blood. The specific gravity falls, red cells and hæmoglobin are lower than before, while the white cells are unaltered, and the plasma is shown to be more watery than before as well as of increased quantity per cubic millimetre. All these changes are less marked in capillary blood, and hence are *rarely observed*.

3. If the heart adjust itself partially to the increased work it has to do, and to the chronic passive congestion of the internal organs and at the periphery, the blood is concentrated, probably in part by transudations into serous cavities and lymph spaces, and in part by the increased excretion of moisture by the lungs. The specific gravity and the number of red cells are increased, *especially in the capillaries*, and to a lesser extent in the venous blood (the conditions being just the reverse of those in acute heart failure, stage No. 2). This is the condition usually found in heart disease with chronic venous stasis (passive congestion).

But this concentrated condition of the blood may be offset from time to time by fresh weakening of the heart and lessen-

ing of blood pressure, and the combination of the two conditions may result in a normal blood count.

The condition of concentrated peripheral blood with the count of red cells above normal, is that most commonly seen in chronic heart disease with stasis.

Von Limbeck finds that aortic lesions are more apt to show a normal or diminished blood count, while mitral disease is more apt to be accompanied by the temporary dilutions and long-standing concentration above described. He does not explain the cause of this. One of his patients with double mitral lesion showed a decrease of 1,170,000 red cells (from 7,500,000 to 6,330,000) after exertion. When the patient was quiet, the lesion was compensated; on exertion compensation temporarily failed, blood pressure was lowered, and the blood diluted.

Sadler[1] found considerable anæmia in three out of four cases of aortic disease, while only two of seven patients with mitral lesions showed anæmia.

Schneider's[2] results were similar in that he found the red cells normal in the aortic cases and increased in the mitral ones.

Hayem found anæmia most common in aortic regurgitation, especially in young people.

In the Massachusetts Hospital records out of twelve cases of mitral disease five had less than 4,000,000 red corpuscles per cubic millimetre. Of three cases of aortic disease all were over 4,000,000. I think these figures simply mean that the mitral cases are more apt to come to the hospital in the stage of acute failure of compensation—therefore (see above) with diluted blood—while the aortic cases often come while compensation is still good and therefore with practically normal blood.

White Corpuscles.

Almost all writers whom I have consulted agree that the leucocytes remain normal unless some complication occurs. In a certain number of the Massachusetts Hospital cases, mostly (but not exclusively) those with cyanosis, the leucocytes were *increased*, the counts ranging sometimes as high as 15,000, while the red cells were normal. I suppose this is to be accounted for by the fact that in any case in which the circulation is feeble and slow, the white cells accumulate at the periphery even more

[1] *Loc. cit.*, p. 33. [2] Inaug. Dissert., Berlin, 1888.

plentifully than the red. This is evidently so in the cases of congenital heart disease next to be mentioned, in which the red cells are increased only about forty per cent, while the white are often one hundred per cent more numerous than normal.

The apparently normal count of red cells in some of our cases was probably due to the covering up of an anæmic or diluted condition of the blood by concentration, the resultant of the two forces being an apparently normal count.

Koblank (*loc. cit.*) gives the following cases illustrating this condition:

	Red cells.	White cells.
1. Mitral leakage................	5,461,250	28,000 + ; autopsy.
2. Aortic leakage................	4,716,600	13,000 +

This leucocytosis must be taken into account in making inferences from cases whose circulations are feeble, and no deeper underlying cause (*e.g.*, abscess, cancer) need be assumed to account for the increase.

Œdema and diuresis have in themselves little or no constant effect upon the blood, as a recent observation of Petrowsky's has demonstrated.

CONGENITAL HEART DISEASE.

In the cyanosis accompanying this affection very high blood counts are reported. Gibson found:

Case.	Red cells.	White cells.	Per cent hæmoglobin.
1..........................	8,470,000	12,000	110
2..........................	6,700,000	12,000	92

Carmichael reports, red cells, 8,100,000, white cells, 16,000, in a single case, and Toeniessen counted 8,820,000 and 7,540,000 in two similar cases. In one case entirely without evidence of any stasis I counted 8,431,000 red cells per cubic millimetre. How such cases are to be explained I do not know; the ordinary explanation of concentration of the blood will not hold in cases in which no stasis or lack of compensation exists, yet the skin is blue and the blood counts are enormous.

There is no doubt that the peripheral capillaries always con-

tain more corpuscles per cubic millimetre than do the veins. Numerous reports from various observers agree upon this. Whether this is on account of the loss of water by perspiration and consequent drain of blood from the skin capillaries is uncertain, but in congenital heart disease both capillary and venous blood is overcrowded with corpuscles and the explanation is difficult.

The most important practical deduction from these data is that a blood count in a patient suffering from poorly compensated heart disease has no value in determining whether or not anæmia is present. The actual number of corpuscles in the body is not measured by the number contained in a drop of peripheral blood, since anæmia may be effectually masked by concentration or simulated by dilution.

This holds good equally for any condition involving *general* stasis and cyanosis either from embarrassment of the heart's action or otherwise (for instance, pneumonia in certain stage, emphysema, displacement of the heart by serous effusions, or tumors), or *local* stasis of the part from which blood is taken. Penzoldt[1] noted that in old hemiplegic cases, the blood from the affected side contained more corpuscles than that from the sound side, and the writer has noticed the same thing in a variety of vasomotor affections involving local asphyxia.

DISEASES OF THE KIDNEYS.

Many factors other than the disease itself may influence the blood of nephritic cases. For instance, in scarlatinal nephritis the long-standing leucocytosis is probably due largely to the scarlatinal poison, rather than to the nephritis. The occurrence of large quantities of blood in the urine has the same influence as any other hemorrhage upon the blood.

Œdema as such has apparently very little effect upon the blood, but the *loss of albumin* in the urine tells both on the corpuscles and on the serum, thinning both with consequent lowering of the specific gravity of the blood.

[1] Berliner klin. Woch., 1881, p. 457.

ACUTE NEPHRITIS.

1. *Red Cells and Hæmoglobin.*

Whether largely from the loss of blood from the kidneys or from other causes, the red cells are often much diminished, but the hæmoglobin suffers still more. Laache reports an average loss of nineteen per cent of the red cells and twenty-six per cent of their coloring matter.

Hayem found no considerable loss of red cells unless the urine was hemorrhagic. The following cases illustrate his results.

CASE I.—Acute nephritis, ending in recovery.

	Red cells.
March 17th, 1882	3,069,000
March 31st, 1882	2,759,000
April 7th, 1882	2,821,000
May 1st, 1882, albuminuria ceased.	
May 17th, 1882	3,038,000
May 31st, 1882	3,689,000

CASE II.—Acute (puerperal) nephritis; recovery.

	Red cells.
April 6th, 1881	2,945,000
" 9th, 1881	2,976,000
" 12th, 1881, no albumin in urine.	
" 13th, 1881	3,137,500
" 20th, 1881	3,310,000

CASE III.—Nephritis (chronic ?) with hæmaturia.

Red cells .... 2,821,000.

(It should be noted that Hayem's counts are low on the average, and the instrument used by him not very reliable.)

Grawitz in acute nephritis records 3,400,000 red cells at the beginning of the third week, and 3,100,000 ten days later.

Koblank[1] counted 5,168,700 in a case of acute nephritis with œdema.

Sadler (*loc. cit.*) in six cases of acute nephritis found in two cases 3,590,000 and 2,262,000 red cells; in the other four practically normal counts.

[1] Inaug. Dissert., Berlin, 1889.

TABLE XXXIV.—ACUTE NEPHRITIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	56	F.	....	22,200	......	Temperature, 102.5°; gradually falling in course of two weeks.
				14,000	......	Sixth day.
				11,900	......	Ninth day.
				12,200	......	Nineteenth day.
2	11	F.	4,068,000	14,000	52	Pale and pasty. Anasarca, ascites, and hydrothorax.
3	....	F.	....	12,000		
4	33	M.	3,904,000	9,300	50	Eczema and purpura also.
5	22	F.	5,000,000	6,000		
6	28	M.	4,944,000	6,400	......	Acute parenchymatous.

In none of the few cases examined at the Massachusetts Hospital were the red cells much diminished, but in two cases the hæmoglobin was very low, the color index being .62 in one and .61 in the other.

The blood plates are much increased (Hayem) and fibrin slightly increased.

2. *White Cells.*

Leucocytosis is the rule, lasting often for weeks at a time and gradually diminishing in convalescence.

Hayem gives counts of 14,973, 12,400, 15,000, and 13,000.

Koblank (*loc. cit.*) and Grawitz each in a single case found *normal* counts (7,300 and 5,600).

Sadler found an increase in only one of his six cases, and then the highest point reached was 13,312.

Of the six cases of Table XXXIV. leucocytosis was present in three, in one of which it was followed for three weeks and still persisted.

CHRONIC DIFFUSE AND CHRONIC PARENCHYMATOUS NEPHRITIS.

Red Cells.

In advanced stages the counts may run very low, but more often it is chiefly the hæmoglobin that suffers through the drain of albuminoids from the blood into the urine.

Hayem gives the following figures:

CASE I.—Chronic parenchymatous nephritis.

	Red cells.	Per cent hæmoglobin.
June 20th	4,309,000	43
July 4th	4,216,000	44
October 18th	2,945,000	34

CASE II.—Same diagnosis.

	Red cells.	Per cent hæmoglobin.
March 6th	2,619,500	36
" 8th	2,836,500	36
" 23d	2,464,500	27

Koblank (*loc. cit.*) in the same disease found 3,291,700 red cells in a single case with much œdema.

Reinert found 4,050,000 with 50 per cent of hæmoglobin and 3,604,000 with 62 per cent hæmoglobin.

Sadler:

	Red cells.
Case 1	4,120,000
" 2	2,405,000—November 19th. 1,100,000—January 14th. 1,500,000—January 17th.
" 3	4,300,000
" 4	4,300,000
" 5	3,737,500—June 28th. 3,593,700—July 3d. 2,187,500—August 15th.
" 6	3,200,000—July 7th. 3,257,000—July 22d. 3,137,000—August 21st.

Grawitz in an acute exacerbation of a chronic parenchymatous nephritis found 1,928,000 red cells.

The Massachusetts Hospital cases show a considerable anæmia in seven out of the twenty-eight, or one-quarter of the series. Great concentration is probably the cause of the very high counts in cases 10, 18, and 22. The majority of cases are not far from normal so far as the number of red cells goes, and the hæmoglobin is also very little diminished; the color index is high.

TABLE XXXV.—CHRONIC DIFFUSE AND CHRONIC PARENCHYMATOUS NEPHRITIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	Adult.	M.	....	18,600	....	Stasis and cyanosis; arteriosclerosis.
2	45	M.	2,648,000	16,300	45	Universal eczema.
3	45	M.	4,400,000	15,000	55	Uræmia.
4	43	M.	5,480,000	14,500	88	Ascites, hydrothorax, asthma.
5	56	F.	4,940,000	14,000	90	Ascites, hydrothorax.
6	66	M.	5,600,000	14,000	85	Adult leucocytes, 72 per cent.
7	27	M.	4,912,000	13,000	64	Much fat in urinary sediment.
8	23	M.	4,380,000	12,500	54	Uræmia, April 3d.
				26,800	....	Convulsion and coma, April 16th. April 17th, died.
9	59	M.	....	12,100	....	Uræmic; vomiting.
10	44	M.	6,936,000	11,300	82	Diarrhœa for five months.
11	49	M.	4,844,000	11,000	78	Uræmic and moribund.
12	43	F.	4,196,000	10,800	50	
13	?	M.	3,780,000	7,750	60	December 28th.
				13,600	....	January 21st, uræmic.
14	27	M.	....	9,000		
15	28	M.	6,000,000	7,600	85	
16	....	...	3,564,000	7,332		
17	41	M.	5,456,000	7,000	75	
18	8	M.	6,800,000	6,800	60	Œdema (!)
19	39	M.	4,552,000	6,500	65	
20	7	M.	3,160,000	6,400	40	
21	....	...	4,572,000	6,250	85	
22	Adult.	M.	1,055,555	5,513		
23	30	F.	3,040,000	5,200	54	
24	30	M.	4,756,000	5,000	65	
25	58	M.	5,512,000	4,800	62	Double aortic murmur; hydrothorax.
26	Adult.	M.	3,256,000	4,500	51	
27	"	M.	3,560,000	3,000	64	Asthma.
28	19	M.	5,900,000	....	82	

White Cells.

Hayem records 25,000, 19,000, 13,000, 10,000, and 6,000 and concludes that the counts vary much not only in different cases but in the same case at short intervals.

Koblank found 14,700 in a single case.

Sadler in one case found 6,300 in November and 16,000 in the following January; 12,000 in another case; 8,800, 7,700, and 1,916 in others.

The same wide range is seen in Table XXXV., in which

thirteen of the twenty-eight cases showed leucocytosis. Of these thirteen six were uræmic. The presence or absence of œdema seemed to make no difference.

CHRONIC INTERSTITIAL NEPHRITIS.

Hayem found the fibrin more increased in this form of nephritis than in any other, and the anæmia less pronounced.

Grawitz distinguishes two stages:

I. As long as the heart is strong enough to overcome the increased resistance at the periphery and the disturbances of circulation are not marked, the blood is normal.

II. When compensatory hypertrophy is no longer sufficient to do the work of forcing the blood through the system, the usual effects of failing compensation (see Heart Disease, page 256) appear (dilution and subsequent concentration of the blood).

The *white cells* are normal.

TABLE XXXVI., A.—CHRONIC INTERSTITIAL NEPHRITIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	39	M.	6,040,000	19,381	80	Uræmic coma; moribund.
2	....	F.	4,548,000	15,000	50	Uræmic; mitral stenosis.
3	Adult.	M.	4,244,000	12,000	67	Three and one-half hours after a meal.
4	46	M.	....	9,724	....	Uræmic; moribund.
5	20	M.	4,088,000	6,000	66	March 23d.
					52	" 30th.

TABLE XXXVI., B.—PYELO-NEPHRITIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	24	F.	3,056,000	21,200	41	March 10th. Uræmia.
			2,976,000	15,200	38	" 13th.
			2,696,000	18,800	33	" 27th.
			3,272,000	25,200	33	April 14th.
2	26	F.	4,200,000	16,800	....	Perinephritic abscess too.
3	33	M.	4,536,000	15,550	36	Cystitis also.
4	26	F.	2,356,000	7,280	65	" "

TABLE XXXVI., C.—CYSTIC KIDNEY.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	55	M.	3,664,000	6,400	....	Adult cells, 72 per cent. Supposed cancer. Enormous firm tumor on each side. Autopsy.

The cases recorded in Table XXXVI., A, are probably not inconsistent with these rules. Of the four cases with leucocytosis three were uræmic, and in the fourth the influence of digestion is seen. The hæmoglobin is lower than we should expect from Grawitz's account.

Uræmia, it would appear from these tables, may cause leucocytosis or at any rate is not infrequently associated with it.

PYELO-NEPHRITIS.

Table XXXVI., B, speaks for itself. The *anæmia* is often severe and leucocytosis is the rule.

STONE IN THE KIDNEY.

(See Table XXXVII., A.) The state of the blood depends on the amount of ulceration caused by the stone; when this is considerable we have leucocytosis.

TABLE XXXVII., A.—STONE IN THE KIDNEY.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	19	M.	....	15,200	....	Much pus in urine.
2	....	M.	4,350,000	14,750	78	
3	25	F.	4,160,000	9,000	65	
4	48	M.	....	8,990		
5	58	M.	5,680,000	8,000		
6	....	....	4,340,000	8,000	....	Much pus in urine.
			6,100,000	16,500	....	Two weeks later.
7	52	M.	3,048,000	7,500	30	

TABLE XXXVII., B.—FLOATING KIDNEY.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo-globin.	Remarks.
1	37	F.	5,056,000	9,200	75	
2	41	F.	4,684,000	9,000	75	
3	23	F.	5,400,000	6,000	69	
4	43	F.	4,700,000	2,400	76	
5	38	F.	....	....	75	Aneurism of arch also.
6	24	F.	....	....	80	

Diagnostic Value.

Cancer would also cause leucocytosis, but would not increase fibrin as a rule, while most cases of stone with ulceration do increase fibrin.

FLOATING KIDNEY.

The blood is normal. This fact has some diagnostic value; for example, when we confound appendicitis with floating kidney, as has been done (see page 201). The presence of leucocytosis excludes the latter and favors the former. Most tumors or abscesses with which a floating kidney might be confused could be distinguished by the same criterion.

DISEASES OF THE LUNGS.

BRONCHITIS.

"Acute catarrhal and chronic purulent bronchitis have relatively little leucocytosis in most cases" (v. Limbeck).

Except for this and a few other passing references, there is hardly anything in literature on the blood in bronchitis, so that I shall be forced to base my statements chiefly on the few counts recorded at the Massachusetts General Hospital.

1. ACUTE BRONCHITIS.

Aside from "capillary bronchitis," cases are not infrequently seen in which the signs are simply those of general bronchitis

of the finer tubes, yet the symptoms are much more like pneumonia. Whatever may be the real conditions in the lungs of such patients, their blood is not infrequently exactly like that of pneumonia and does not help at all in the differential diagnosis between the two diseases (see Cases 1 and 2, Table XXXVIII., A).

TABLE XXXVIII., A.—ACUTE BRONCHITIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	70	M.	4,420,000	41,000	70	
2	56	F.	4,800,000	26,000	65	Temperature 103°. Râles on both sides alike; no consolidation.
3	Adult.	F.	4,192,000	15,000	65	November 5th.
				11,300	....	" 16th.
				17,600	....	" 25th.
4	28	F.	6,096,000	12,000	65	Cyanosis? Much purulent expectoration.
5	42	M.	....	9,300	....	Asthma.
6	Adult.	...	5,260,000	8,000	72	Neurosis.
7	50	M.	5,952,000	7,992	50	
8	59	F.	....	6,800	....	Emphysema.
9	36	M.	4,392,000	6,000	72	October 31st.
				8,600	....	November 3d.

TABLE XXXVIII., B.—CHRONIC BRONCHITIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	Adult.	M.	3,680,000	18,500	63	
2	48	M.	....	15,000	....	Chronic febrile, with laryngitis. Recovery.
3	27	F.	5,384,000	8,800	73	Constipation; neurasthenia; two weeks afebrile.
4	61	M.	4,300,000	8,000	63	Five months.
5	20	F.	....	7,925	78	
6	18	M.	....	7,792	....	Keratitis, conjunctivitis. No symptoms.
7	26	F.	4,700,000	6,700	70	Asthma.
8	29	F.	4,100,000	5,500	61	Empyema of the antrum.
9	20	M.	....	5,062	....	One month.

In the majority of acute cases, however, the blood shows no changes unless concentration due to cyanosis be present (see Cases 4 and 7, Table XXXVIII., A).

In chronic cases (Table XXXVIII., B) leucocytosis is very uncommon, more so, I think, than the table represents. If more counts were added, nearly all, I think, would be normal.

The red cells and hæmoglobin show no changes to speak of in either acute or chronic cases.

The blood has no diagnostic value so far as I know except that when pneumonia is in question a normal count of white cells speaks against it and in favor of bronchitis. If emphysema is also present it sometimes produces a different blood condition from that of simple bronchitis.

EMPHYSEMA AND ASTHMA.

Grawitz reports an increase in the number of red cells in *emphysema*, which he believes to be due to cyanosis and to cover up the really anæmic condition of the blood of many patients. Practically the same conditions are present as in the cyanosis of heart disease (see page 256) and the concentration of the blood is brought about in the same way. Leichtenstern[1] noticed a diminution in hæmoglobin at the time when the heart first fails, due probably to the diminished blood pressure which allows the lymph from neighboring tissues to flow into the vessels and dilute the blood.

In both asthma and emphysema it has been noted by Müller,[2] Gollasch,[3] Gabritschewsky[4] and others that *eosinophiles* are very numerous in the sputum, and Fink[2] also noted an increase of the same cells in the blood, running as high as 14.6 per cent instead of the normal one to two per cent. This increase is present only at the time of the paroxysm and for a short time before and after it. Their presence in increased numbers before a paroxysm makes it possible to predict its coming (v. Noorden, Schwerskewski). As this applies only to pure *bronchial asthma* and not to cases secondary to disease of the heart or kidney, Schreiber states that we are enabled to distinguish bronchial from cardiac or renal asthma by the increase of eosinophiles in

[1] "Ueber das Hb-Gehalt des Blutes," etc., Leipzig, 1878.

[2] Ref. in Fink, "Beiträge z. Kennt. des Eiters," Dissert., Bonn, 1890.

[3] Fortschritte der Med., 1889.

[4] Arch. f. exp. Path. und Pharm., 1890, p. 83.

the blood and sputa in bronchial cases, which does not occur in asthma due to cardiac and renal trouble.

For Pneumonia, see page 159.

For Phthisis, see page 219.

For Abscess of Lung, see page 207.

PART V.

DISEASES OF THE NERVOUS SYSTEM, CONSTITUTIONAL DISEASES, AND HEMORRHAGIC DISEASES.

CHAPTER VIII.

DISEASES OF THE NERVOUS SYSTEM.

NEURITIS.

In a single case of multiple neuritis, febrile and apparently of an infectious nature, the following counts are found in the records of the Massachusetts General Hospital:

Date.	Temperature.	Red cells.	White cells.	Per cent hæmoglobin.
July 10th..........	101°................	4,816,000	25,000	42
" 13th..........	....	....	24,800	
" 16th..........	....	....	18,700	
" 20th..........	....	....	21,000	
" 25th..........	....	4,320,000	16,000	60
" 31st..........	(No fever.)..........	....	28,700	
August 7th........	" "	....	19,500	
" 20th.......	" "	....	23,200	

The patient, a boy of eleven, recovered and left the hospital well.

But these changes occur also in alcoholic (afebrile) neuritis, as the following counts show.

Case.	Red cells.	White cells.	Per cent hæmoglobin.
1..........................	3,608,000	15,000	75
2..........................	3,260,000	14,000	64

In both cases the counts were made just at mealtime, so that the leucocytosis is not due to digestion. Gastritis was not present in either case.

One case of post-diphtheritic neuritis in a child of eight showed the presence of anæmia only: Red cells, 3,850,000; white cells, 7,393; hæmoglobin, 70 per cent.

Neuritis in lead poisoning does not affect the count of leucocytes.

Neuralgia, whether facial, intercostal, sciatic, or ovarian, showed normal blood in numerous cases examined at the Massachusetts Hospital.

DISEASES OF THE BRAIN.

Meningitis (see Inflammation of Serous Membranes, page 215).

Zappert in one case of *brain abscess* found only 4,000 white cells.

In *pachymeningitis hæmorrhagica* and *cerebral syphilis* (one case of each) v. Jaksch found leucocytosis.

Cerebral and cerebellar tumors have no effect on the blood as far as could be judged from four counts in the former and two in the latter disease. Von Jaksch found slight leucocytosis in two cases of brain tumor and one of *cysticercosis*. Zappert found normal blood in one case of cerebral tumor.

CHOREA.

Chorea showed in five cases normal blood except for increased percentages of eosinophiles, as in Zappert's two cases.

DISEASES OF THE SPINAL CORD.

Chronic diseases of the spinal cord, such as tabes dorsalis, syringomyelia, spastic paraplegia, diffuse myelitis, paralysis agitans, and progressive muscular atrophy, are found to produce no changes in the blood.

For Spinal Meningitis, see page 216.

GENERAL PARALYSIS OF THE INSANE.

Capps[1] has made a careful study of the blood in nineteen cases and comes to the following conclusions:

[1] American Journal of the Medical Sciences, July, 1896.

1. Red corpuscles and hæmoglobin are always slightly diminished, the averages being 4,789,900 and 85 per cent.

2. Most cases show a slight leucocytosis—22 per cent above the normal on the average. Early cases may have no leucocytosis.

3. The differential counts show that the blood is slightly *older* than that of normal adults. The adult leucocytes average nearly 74 per cent and the smaller forms of young cells only 14.2 per cent, while the larger forms of young cells (large lymphocytes) are relatively numerous, averaging 7.8 per cent. In a few cases the eosinophiles were very numerous[1] (8.7 and 6.4 per cent).

4. At the time of *convulsions* the red cells and hæmoglobin are apparently increased (due no doubt to the violent muscular contractions which raise blood pressure and concentrate the blood, or to cyanosis).

There is a sudden and pronounced increase in the leucocytes during and after convulsions or apoplectiform attacks. That this is not due to concentration of the blood or to stasis Capps thinks is shown by the fact that not only the number but the differential count of white cells show changes, the "*large mononuclear*" *cells being relatively increased*, sometimes as high as 25 per cent. *Myelocytes* were seen in one case after the convulsions, and especially just before death when in a leucocytosis of 18,250 11 per cent were myelocytes.[2]

HYSTERIA AND NEURASTHENIA; HYPOCHONDRIASIS.

A large number of cases have been counted at the Massachusetts General Hospital, with a view to excluding other diseases. The blood count is always normal except that in a certain number of the hysterical cases eosinophiles are relatively increased, and that many of the neurasthenics show the increased percentage of young leucocytes which I have alluded

[1] Roncoroni (Archiv. di Psichiat. Scien., 1894, p. 293) finds eosinophiles increased even to twenty-five per cent in the agitated and violent cases.

[2] Leucocytosis has been repeatedly noticed in convulsions from various causes. Probably the irritant which causes the motor discharge also acts on the leucocytes by chemotaxis.

to above (page 82) as characteristic of a variety of debilitated conditions.

Marked anœmia is seldom present, although the hæmoglobin is not infrequently as low as 65 per cent. Reinert[1] found the hæmoglobin under 60 per cent in only 4 out of 48 cases of hysteria, and in *none* of 36 neurasthenics.

The value of the blood examination in such cases, like that of the urine or the lungs in hysteria, is as negative evidence, and in this respect it is important. When the discrepancy between complaints and signs is great, we want to be doubly sure that nothing hidden escapes our notice, and the blood examination is one of the most valuable adjuvants we have in the discovery of deep-seated inflammation or malignant disease, as well as in giving us a general measure of the patient's degree of bodily health as distinguished from nervous force. The former may be high when the latter is low, or both may be low, and the distinction marks out two classes of cases in which somewhat different treatment is appropriate. There is no use in undertaking to make "blood and fat" when the patient has already plenty of each, though it may be well to carry out the same *régime* as a matter of suggestion.

MENTAL DISEASES.

The association of anæmia with insanity is too frequent to be a mere coincidence, though it is hard to make either serve as a cause for the other. Very possibly they should both be looked upon as symptoms of a common underlying (unknown) cause.

This form of anæmia has been noticed by Houston[2] in melancholia and general paralysis, and by Smith[3] in various forms of insanity.

Krypiakiewicz[4] noticed an increase of eosinophiles in acute forms of insanity but not in the chronic forms. The *leucocytosis of acute delirium*[5] is exemplified by the following case from the Massachusetts Hospital records:

[1] Münch. med. Woch., 1895, No. 14.

[2] Houston: Boston Med. and Surg. Journal, January 11th, 1894.

[3] Smith: Jour. of Ment. Sc., October, 1890.

[4] Krypiakiewicz: Wien. med. Woch., 1892, No. 25.

[5] Ref. in Klein-Volkmann's "Sammlung klin. Vorträge," December, 1893.

A girl of fifteen; acute delirium; leucocytes, 12,750; no food for eight hours; red cells, 4,510,000; hæmoglobin, 63 per cent.

Puerperal mania is to be distinguished from the delirium of puerperal sepsis by the fact that the latter shows leucocytosis with increased percentage of adult cells, while the former has no leucocytosis (if uncomplicated) and the eosinophiles are apt to be increased[1] (diminished in sepsis).

A case of puerperal mania seen by the writer showed: Red cells, 5,210,000; white cells, 6,500; hæmoglobin, 84 per cent; eosinophiles, 8 per cent.

CONSTITUTIONAL DISEASES.

OBESITY.

Oertel distinguishes a plethoric and an anæmic form of obesity not merely clinically but by the evidence of post-mortem examinations. He believes that there is a real over-filling of the vessels in the first. The second form occurs most often in women.

Kisch examined (with v. Fleischl's instrument) the hæmoglobin of 100 obese patients; 79 showed over 100 per cent of hæmoglobin, 1 reaching 120 per cent, while the other 21 were anæmic.

DIABETES.

There is nothing characteristic about the blood except the increased amount of sugar to be detected (.57 per cent as against .1 normally); but this is not a clinically applicable test.

The alkalinity has been said to be greatly diminished, especially in the fatal coma, but v. Noorden thinks the tests are unreliable.

Fat is often *much* increased in the blood, so that the serum is milky, and glycogen has been demonstrated microchemically in the corpuscles.

Red Cells.

Sugar in the blood draws water from the tissues into the vessels, thereby *diluting the blood;* but in a short time the blood

[1] Neusser: *Loc. cit.*

frees itself of the excess of sugar and fluid through increased diuresis so as to *concentrate the blood.*

These two alternating influences serve to explain the widely different counts of different observers.

Toward the end of the disease a decided *cachexia* often develops, the anæmia of which may be temporarily covered up by the concentration above noted, or accentuated by the *dilution* which sometimes occurs. Accordingly we may find the corpuscles increased, normal, or diminished in different cases or at different times with the same case.

Grawitz counted 4,900,000 red cells in a patient in comparatively good health, and three weeks later, when the patient had just been seized with the fatal coma, the count showed 6,400,000 per cubic millimetre.

The white cells show no constant changes, except that v. Limbeck has noted in several cases that the digestion-leucocytosis is unusually large even without previous fasting. Von Jaksch found leucocytosis in one of his eight cases, but on this point as on many others his results are almost unique. The only similar observation is that of Habershon,[1] who reports moderate leucocytosis, decreased by strict diet.

GOUT.

A few cubic centimetres of serum from gouty blood made acid with acetic acid (six drops of a twenty-eight-per-cent solution to every drachm of serum) deposit crystals of uric acid on a thread in from eighteen to forty-eight hours; but this is not always to be found, and is by no means peculiar to gout.[2] Uric acid is to be found in the blood in pneumonia, cirrhotic liver, nephritis, grave anæmia, leukæmia, and gravel; also in health and after a meal of calf's thymus or any food containing much nuclein.

The red corpuscles show no special changes except in severe chronic cases which are sometimes anæmic. The white cells are increased according to Neusser, while v. Limbeck and Grawitz found the blood wholly normal.

[1] St. Bartholomew Hosp. Rep., 1890, p. 153.

[2] It is important to evaporate the serum at a temperature not above 70° F., otherwise crystals will not form.

It is particularly in this disease that Neusser finds the perinuclear basophilic granulations in the white cells, which he believes to be characteristic of any "uric-acid diathesis." Fibrin is increased in acute cases.

MYXŒDEMA.

Le Breton[1] examined the blood in one case before and after thyroid treatment and found after forty days' treatment that the red cells had risen from 1,750,000 to 2,450,000, the white from 4,500 to 9,600, and the hæmoglobin from 65 to 68 per cent.

The remarkably high color index in this case before treatment (nearly 2. !) corresponds with the observations of Le Breton in the dried specimen, which showed a decided increase in the size of the red corpuscles. He also noticed before instituting the thyroid treatment the presence of nucleated red cells and an excess of the adult form of leucocytes. Under treatment the nucleated red cells disappeared and the young forms of leucocytes rose to their normal per cent.

Putnam[2] has watched a similar case in which the red cells rose from 3,120,000 to 5,700,000 under thyroid treatment.

Murray[3] has collected 23 cases with blood examinations. Of these 7 showed normal blood, 10 were anæmic, 4 had leucocytosis, and 2 had both anæmia and leucocytosis.

Kraepelin[4] noticed (like Le Breton) a marked increase in the average diameter of the corpuscles in three cases, even when the count and the hæmoglobin were normal.

I have had an opportunity to examine the blood in three cases of this disease, but did not find anything remarkable in any of them.

Case.	Red cells.	White cells.	Per cent Hæmoglobin.
1	4,670,000	6,000	87
2	4,460,000	8,800	..
3	4,856,000	5,200	80

[1] Le Breton: Ref. in Wien. med. Blätter, 1895, p. 49.

[2] Putnam: Ref. in Murray's article in "Twentieth Century Practice of Medicine," vol. iv.

[3] Murray: "Twentieth Century Practice of Medicine," vol. iv., p. 710.

[4] Kraepelin: Deut. Arch. f. klin. Med., vol. xlix., p. 587.

Differential counts were made in three cases and no increase in the size of the corpuscles, such as Le Breton and Kraepelin saw, was present in these cases. The count showed:

Case.	Adult cells.	Young cells.	Eosinophiles.
1	67	28	5
2	67	27.8	4.4
3	74	26	

The increase of eosinophiles in two of these cases may perhaps be due to the skin troubles present in the disease.

J. J. Thomas found a few myelocytes in a case of Putnam's.

GRAVES' DISEASE (BASEDOW'S DISEASE; EXOPHTHALMIC GOITRE).

The blood is normal, except for an occasional associated chlorosis and sometimes a marked lymphocytosis. In one case I found 51.3 per cent of young cells and 1 per cent of myelocytes in 1,000 leucocytes, the adult cells being only 48 per cent; but in fourteen other cases I have never found this again. The same fact has been noticed by Neusser (cited in Klein, *loc. cit.*).

Oppenheimer[1] found the red cells and hæmoglobin normal in two cases. Von Jaksch[2] in one case "complicated with myxœdema" found 3,818,000 red and 8,000 white cells.

The association of Graves' disease with chlorosis is illustrated by two cases from Zappert:[3]

Case.	Red cells.	White cells.	Per cent hæmoglobin.
1	2,858,000	3,800	32
2	2,738,000	3,800	30

The same writer found eosinophiles much increased (8.5 per cent) in one out of four cases.

ADDISON'S DISEASE.

Some, but not all, cases are accompanied by marked anæmia. Neumann[4] observed a case in which the symptoms came on

[1] Deut. med. Woch., 1889, p. 861.

[2] Zeit. f. klin. Med., 1893, p. 187.

[3] Zeit. f. klin. Med., 1893, p. 266.

[4] Neumann: Deut. med. Woch., 1894, p. 105.

acutely and the red cells sank to 1,120,000 per cubic millimetre. During the convalescence which followed the cells ran up above normal, reaching 7,700,000.

Tschirkoff[1] reports two cases in which the red cells were respectively 3,280,000 and 2,933,000 at the lowest, but whose hæmoglobin was extraordinarily high, over 100 per cent in one case. This he found on spectroscopic examination to be due to a great increase of reduced hæmoglobin in the corpuscles. Methæmoglobin was also noted.

The white corpuscles showed no changes, quantitative or qualitative, except that they contained black pigment granules. Two cases have been examined at the Massachusetts Hospital. The first, a woman of thirty, showed 6,240,000 red cells with 14,000 white, and 90 per cent of hæmoglobin. The differential count of 900 leucocytes showed the following figures: Adult cells, 53.4 per cent; young cells, 41 per cent; eosinophiles, 4.5 per cent; myelocytes, .9 per cent.

The eosinophiles were very large, some of them eosinophilic myelocytes.

The second case was very anæmic and weak at entrance and showed the following condition: Red cells, 2,196,000; white cells, 7,500; hæmoglobin, 20 per cent. Differential count of 200 leucocytes showed: Adult cells, 65 per cent; young cells, 31.5 per cent; eosinophiles, 3.5 per cent.; five normoblasts; marked poikylocytosis.

Under suprarenal extract his blood improved in a month till his red cells numbered 4,700,000, white cells, 9,000; hæmoglobin, 65 per cent.

A third patient, kindly sent me by Dr. Rogers, of Dorchester, showed: Red cells, 2,864,000; white cells, 2,000; hæmoglobin, 51 per cent. Differential count of 300 cells showed: Adult cells, 63.3 per cent; young cells, 33.3 per cent; eosinophiles, 2.3 per cent; basophiles, .3 per cent.

I have never seen melanin in the leucocytes as Tschirkoff did in his two cases.

OSTEOMALACIA.

The blood has for a long time been supposed, on the authority of v. Jaksch (*Zeit. f. klin. Med.*, Vol. 13, page 360), to exhibit

[1] Zeit. f. klin. Med., 1891, vol. xix., Suppl. Heft 37.

a diminished alkalinity, the bones being supposed to be eaten away by acids in the blood. Von Limbeck and many other observers have lately shown that the blood is normal in alkalescence.

Corpuscles and hæmoglobin are usually within normal limits quantitatively, but Neusser reports an increase of eosinophiles and the presence of myelocytes in the blood.

Ritchie[1] confirms Neusser and found also the young leucocytes more numerous than normal.

Fehling,[2] Sternberg,[2] Chrobak[2] found no increase of eosinophiles.

Rieder's case was normal in all respects: Red cells, 4,892,000; white cells, 5,600; eosinophiles, 3.6 per cent; adult cells, 61 per cent.

RICKETS.

1. Anæmia is always present in severe cases and often in moderate ones. This, together with the fact that many cases of rickets are associated with an enlargement of the spleen, has led to the use of the misleading term "splenic anæmia."

Hock and Schlesinger found an average of 2,500,000 red cells in a considerable number of cases with and without enlarged spleen.

Von Jaksch describes a case in which the red cells sank from 1,600,000 to 750,000 within three months, and Luzet saw a similarly rapid process, the cells falling from 2,110,000 to 1,596,000 within three weeks.

2. Apparently the hæmoglobin per corpuscle is normal—that is, the color index is not low. Monti and Berggrün found 40–50 per cent hæmoglobin with 3,148,000 red cells and Hock and Schlesinger 60 per cent hæmoglobin with 2,300,000 cells.

White Corpuscles.

It is often difficult to say whether or not the leucocytes are increased, owing to the occurrence of most cases in infants at an age when leucocytes are always higher than in adults—how much higher at any given age depends largely upon the degree of

[1] Edin. Med. Journal, June, 1896.
[2] Cited by Ritchie (*loc. cit*).

vigor and forwardness of development of the individual child. At any rate, the counts are usually from 15,000 to 40,000 with considerable variations from week to week.

Qualitative Changes.

Red Cells.

As in all anæmias of infants, the "degenerative" and "regenerative" changes are relatively common.

Polychromatophilic forms and nucleated corpuscles are frequently to be found, the latter often in great numbers but with a majority of the normoblast type.

White Cells.

Lymphocytosis is marked, but, as with the question of leucocytosis, we are never quite sure whether the numbers are abnormal *for that age*, for lymphocytosis is the normal condition in infants' blood.

When, however, as in a case mentioned by Rieder, we find 75 young cells in every 100 leucocytes, the child being four years old, we are surely dealing with a pathological condition. Another of his cases, a seven-months' child, rachitic, with 57 per cent of young leucocytes, seems to fall within normal limits. The same difficulty arises with regard to the reports of *eosinophilia* in rickets, since eosinophiles are always relatively numerous in infancy. In Rieder's four cases and in the three seen at the Massachusetts Hospital, no eosinophilia was present. Myelocytes in small number (.5–2. per cent) are not uncommon, and may be considerably more numerous.

CHAPTER IX.

BLOOD DESTRUCTION AND HEMORRHAGIC DISEASES.

1. PURPURA HÆMORRHAGICA.

THE blood is practically that of anæmia from hemorrhage (red cells and hæmoglobin reduced, white cells increased, occasional nucleated red corpuscles or polychromatophilic forms). Agello[1] has found methæmoglobin in the blood, and hence concludes that the disease is a poisoning of the corpuscles by ptomains absorbed from the intestine.

The blood plates are much diminished and may be entirely absent in the worst stages.

Bacteria of various kinds have been reported in the disease, but negative results are also common, and their presence is probably not significant.

The red cells may fall as low as 2,500,000, but are much oftener slightly or not at all diminished. In many mild cases there are *no* demonstrable blood changes. On the other hand, Osler mentions a case which sank to 1,800,000.

SCURVY.

There are no characteristic blood changes known. When hemorrhage is severe the red cells may sink very low, to 557,875 in a case of Bouchut's; Ouskow and Hayem saw counts of 3,500,000 and 4,700,000. The usual qualitative changes of secondary anæmia are present in severe cases; hæmoglobin suffers as usual more than the count of red cells.

Leucocytes are generally increased, whether from hemorrhage or from some complicating inflammatory process.

Barlow's disease may lower the red cells as far as 976,000—

[1] Riforma Med., Napoli, 1894, p. 103.

as in a case of Reinert's—the hæmoglobin being seventeen per cent and the white cells 12,000. This was the day before death.

HÆMOPHILIA.

The blood changes are practically those just described and show nothing characteristic of the disease. Coagulation is slower than normal and blood plates are sometimes very scanty.

BLOOD DESTRUCTION (HÆMOCYTOLYSIS).

I. Besides the slow destruction of corpuscles which takes place in any ordinary anæmia, we have a group of conditions under which a large number of red cells are suddenly destroyed in the circulation itself. This may take place by—

1. Separation of the hæmoglobin from the corpuscles so that it colors the serum.

2. Actual breaking to pieces of the red cells without separation of the hæmoglobin.

If normal blood is drawn and left to stand, the serum which separates from the corpuscles is not red-tinged or but very slightly so, *provided* all shaking and jarring are avoided. A very slight reddish tinge may appear in the serum even with most careful technique. In some conditions the hæmoglobin, while not actually separated from the corpuscles within the vessels, is so loosely connected to them that a considerable quantity separates post mortem and colors the serum in spite of the avoidance of any jar.

This condition is to be distinguished from true hæmoglobinæmia, in which the serum is actually colored before leaving the vessels, although the two conditions really represent only different degrees of vulnerability of the red cells.

We are surer of a diagnosis of hæmoglobinæmia when we find bits of broken-down cells in the fresh blood and the additional evidence of hæmoglobinuria or jaundice.

1. Severe forms of malaria, yellow fever, typhus fever, severe forms of septicæmia, and rarely scarlet fever may cause hæmoglobinæmia.

2. *Paroxysmal hæmoglobinæmia,* so-called, is a variety whose cause is unknown and which does not seem secondary to any

other disease, unless a certain relationship to syphilis be established, and possibly to malaria. The attacks are brought on by a great variety of causes (cold, muscular or mental strain, etc.). Some persons can always bring on an attack by putting the hand or foot into cold water.

Blood Examination.

Coagulation is very rapid, but the clot soon dissolves again (Hayem). The fresh blood shows deformities in the corpuscles and bits of broken cells, if examined during a paroxysm. The following figures from Grawitz illustrate the loss of cells from a single paroxysm. Before the paroxysm: Red cells, 4,750,000; white cells, 12,000. Toward the end of the paroxysm: Red cells, 3,620,000; white cells, 12,000.

Hæmoglobin is decreased equally with the red cells. The loss is soon made up again in most cases, and between the paroxysms we may find normal blood or only a slight anæmia. The leucocytes are normal.

The serum is brilliantly red-colored at the time of the paroxysm.

All that is known of the disease is expressed by saying that for *some reason* the red cells are abnormally *sensitive*, so that any one of a variety of slight disturbances is sufficient to separate their hæmoglobin and set it loose in the plasma.

3. Extensive *burns* have been reported to cause hæmoglobinæmia with breaking up of the red cells, presumably through changes in the serum similar to those which make duodenal ulcer so common a sequel to bad burns.

4. Snake poison and scorpion poison may have similar effects.

II. Another group of corpuscle destroyers is that which works by changing the *hæmoglobin* to *methæmoglobin*. The most important of these is—

1. *Chlorate of Potash.*—This destroys the corpuscles and produces hæmoglobinæmia and the usual train of symptoms (jaundice, dark urine, etc.) due to this.

Brandenburg[1] examined the blood of a woman who had taken two and one-half ounces of chlorate of potash in water the night before. The blood showed *marked* leucocytosis, broken and

[1] Berliner klin. Woch., 1895, No. 27.

distorted red cells. In gross it was chocolate-colored and the serum after separation of the clot was brown. The red cells progressively decreased as follows:

	Red cells.	White cells,
First day	4,300,000	20,000
Second day	2,500,000	
Fourth day	2,300,000	
Fifth day	2,100,000	
Sixth day	1,900,000	
Seventh day	1,600,000	15,000 (death).

2. *Antipyrin and antifebrin* in doses of thirty to forty-five grains may cause great cyanosis and dangerous prostration through transformation of the hæmoglobin and methæmoglobin. In certain persons much smaller doses produce the same effect.

3. *Phenacetin poisoning* (Kronig: *Berl. klin. Woch.*, 1895) may cause actual blood destruction with anæmia in case the patient survives the immediate effects of the deprivation of oxygen.

4. *Phosphorus poisoning* (see Liver, page 251).

5. Workers in aniline dyes and nitroglycerin factories may be severely poisoned by *nitrobenzol* compounds inhaled and producing methæmoglobinæmia.

6. *Pyrogallic acid and pyrogallol* as used in treatment of skin diseases may lead to death through destruction of the red cells. Chromic acid (for instance, as applied through the vagina) may have a similar effect.

Many other less common substances work the same ill-effects on the blood.

III. A third group of substances, of which *carbonic oxide gas* is the type, poison by combining chemically with the hæmoglobin and preventing its combination with the oxygen of the air.

1. *Illuminating gas* is for our purposes the most important of this group, with carbonic oxide gas second.

The appearance of individual blood cells is not altered nor do they break up, but the corpuscles are useless to breathe with, as they cannot take up oxygen.

The color of the blood is very *bright* red, much brighter than normal.

Red Cells.

Von Limbeck[1] found in two cases 6,630,000 and 5,700,000 respectively. The *volume* of these corpuscles (estimated by Bleibtreu's method) was greatly increased, amounting to 70.7 per cent (normal 41–48 per cent), so that apparently the size of the individual cells is increased.

Münzer and Palma[2] found 5,700,000 red cells in one case.

Leucocytes.

Eaton[3] reported four cases, in all of which the white cells were increased, the counts ranging between 15,000 and 22,000 per cubic millimetre.

Münzer and Palma (*loc. cit.*) found 13,300 in their case. Two such cases have been examined at the Massachusetts Hospital with the following results:

Case.	Red cells.	White cells.	Remarks.
1	4,930,000	17,500	
2	....	21,200	November 27th, comatose.
		15,500	November 29th, convalescent.

Warthen[4] reports the same condition in a single case. Here the specific gravity was also very high (v. Limbeck finds that this is to be explained by the increase in the actual size of the corpuscles).

When there is any doubt as to diagnosis, the following test will settle it: Shake a small quantity of fresh-drawn blood into three times its volume of subacetate of lead. If the blood contains CO the mixture becomes of a fine red color; otherwise it turns chocolate-colored.[5]

2. Da Costa (*Med. News*, March 2, 1895) reported a consider-

[1] *Loc. cit.*, p. 234.
[2] Zeit. f. Heilk., vol. xv., p. 1.
[3] Boston Medical and Surgical Journal, March 14th, 1895.
[4] Virchow's Archiv, vol. cxxxvi.
[5] Rubner: Zeit. f. anal. Chemie, xxx., p. 112.

able diminution in hæmoglobin of patients during *etherization*, especially anæmic patients, but the investigations of Lerber[1] do not confirm this.

Tansy Poisoning.—A single case examined at the Massachusetts General Hospital showed: Red cells, 4,600,000; white cells, 21,000; hæmoglobin, 70 per cent.

[1] Inaug. Dissert., Basel, 1896.

PART VI.

MALIGNANT DISEASE, BLOOD PARASITES, AND INTESTINAL PARASITES.

CHAPTER X.

MALIGNANT DISEASE.

The Blood as a Whole.

1. The specific gravity is reduced in most cases, running roughly parallel with the hæmoglobin.
2. Coagulation is normal or slower than normal in uncomplicated cases. When sloughing and inflammation are present it may be rapid.
3. Fibrin is usually normal; an increase means inflammation in or around the tumor or an inflammatory complication.

CANCER.

Red Corpuscles.

As in tuberculosis, we are frequently surprised to find but little diminution in the number of red cells. In all but very advanced cases this is the rule. It is a change of the individual red cells (pallor, loss of size, of weight, degenerative changes), rather than a reduction of numbers.

Nevertheless in the later cachectic stages of most cases of malignant disease, we do find a quantitative anæmia, the counts often running as low as 2,500,000 and occasionally sinking as low as in pernicious anæmia. Thus v. Limbeck records a case (complicated by repeated hemorrhages) with only 950,000 red cells per cubic millimetre. The lowest of my own cases was 1,632,000 per cubic millimetre.

There seems to be no considerable difference between cancer and sarcoma as regards their effect on the red cells.

TABLE XXXIX., A.—GASTRIC CANCER WITHOUT LEUCOCYTOSIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	42	M.	6,040,000	4,400	48	
				7,200	....	One week later; mealtime, April 14th.
				8,900	....	Four hours after meal.
				5,140	....	April 16th, mealtime.
				4,400	....	April 16th, three and one-half hours later.
				6,500	....	April 17th, mealtime.
				6,058	....	April 17th, three hours after.
2	59	M.	3,900,000	5,000		
3	71	F.	5,880,000	4,800	90	
4	63	M.	3,470,000	5,000		
5	71	M.	3,744,000	5,200		
6	54	F.	4,772,000	5,600		
7	63	M.	5,040,000	6,000	....	Operated.
8	54	M.	5,200,000	6,000	42	
9	52	M.	3,200,000	5,200	25	Operated.
10	34	M.	2,296,000	6,150	27	July 28th, 1895, before eating.
				5,650	....	July 28th, 1895, three and one-half hours after eating.
				10,600	....	July 20th. In 500 white cells; polymorphonuclear, 78 per cent; small lymphocytes, 13; large lymphocytes, 9. No nucleated red cells.
11	Adult.	F.	1,940,000	6,660	26	December 12th, 1895.
			1,947,000	8,000	22	January 8th, 1895.
12	Adult.	M.	4,612,000	6,300	70	
13	52	F.	3,680,000	6,327	33	No nucleated red cells. Slight poikylocytosis.
14	43	M.	5,472,000	6,500	78	
				6,527	....	Ten days later, mealtime.
				5,306	....	Ten days later, four hours after meal.
				10,180	....	Eleven days later, mealtime.
				8,886	....	Eleven days later, four hours after meal.
15	39	M.	5,000,000	6,500	80	Considerable dilatation.
16	34	F.	5,480,000	7,000	75	November 18th, 1895. Considerable dilatation.
				4,500	....	December 2d, 1895, before meal.
				8,000	....	December 2d, 1895, four hours after meal.
17	47	M.	3,168,000	7,300	38	
18	68	M.	4,880,000	7,600		
19	33	M.	3,200,000	8,000		
20	Adult.	M.	4,632,000	8,400	45	Autopsy.
21	52	F.	6,928,000	8,600	78	In 1,000 white cells: 62.5 per cent polymorphonuclear; 21 small lymphocytes; 15.5 large lymphocytes; 1 eosinophiles. Autopsy, one month later.
22	48	M.	3,708,000	8,750	43	
				13,225	....	One month later, before meal.
				12,175	....	One month later, four hours after meal.
23	51	M.	3,860,000	9,250	58	December 26th.
				11,370	....	January 10th, 1:30 P.M.
				12,100	....	January 10th, 5 P.M.
24	66	M.	3,704,000	9,391	50	
25	Adult.	M.	....	9,600	....	400 white cells show polymorphonuclear, 62 per cent; small lymphocytes, 24; large lymphocytes, 10; eosinophiles, 4.
26	40	M.	4,460,000	9,750	60	
				9.330	....	Four hours after meal.
27	56	M.	2,928,000	9,800	35	September 27th. Hæmoglobin: August 21st, 44 per cent.; September 1st, 46; September 6th, 52.
28	Adult.	F.	2,400,000	10,000		
29	Adult.	M.	5,120,000	10,500	86	
30	44	M.	2,984,000	10,600	25	

TABLE XXXIX., B.—GASTRIC CANCER WITH LEUCOCYTOSIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
32	65	M.	4,280,000	11,000		
33	61	M.	3,680,000	12,000		
34	53	M.	5,992,000	12,000		
35	Adult.	M.	6,296,000	12,000		
36	Adult.	M.	5,512,000	12,400		
37	Adult.	M.	5,152,000	12,400		
38	56	F.	....	14,700		
39	46	M.	4,640,000	15,000		
40	41	M.	4,150,000	16,800		
41	59	M.	4,240,000	19,200	25	Differential count: Poly., 80 per cent; lymphocytes, 16; eosinophile, 4. September 30th, 1895.
			3,928,000	14,800	30	October 17th.
			3,160,000	15,200	16	October 27th.
			2,256,000	27,000	11	Differential count: Poly., 96 per cent; lymphocytes, 3; eosinophiles, 1; normoblasts, 2; megaloblasts, 2. Died February 24th, 1896. Autopsy.
42	50	F.	4,308,000	16,300	70	November 25th, 1895.
				15,950	....	December 3d, before proteid meal.
				14,170	....	December 3d, three hours later.
				10,000	....	December 19th. Differential count of 300 cells: Poly., 75.7 per cent; small lymphocytes, 18.7; large lymphocytes, 4.3; eosinophiles, 1.3.
				10,300	....	January 8, 1896.
			2,516,000	40,000	30	April 13th, 1896. Differential count of 300 cells: Poly., 86.5 per cent; lymphocytes, 13.5.
			1,632,000	15,950	18	April 26th. Died May 1st. Autopsy.
43	53	M.	4,700,000	19,142	54	Supposed pernicious anæmia.
44	47	M.	3,800,000	19,800		
45	59	M.	4,700,000	32,500	50	
46	40	M.	5,900,000	36,400		
			5,400,000	39,000	....	One week later.

As will be seen by consulting Tables XXXIX., A, B, the count of red cells is sometimes above normal, doubtless due to concentration of the blood from some cause. Probably the same influence is at work in other cases, and many of those showing normal counts have really fewer red cells than they should. Such abnormally high counts are not rare, as the following examples show:

Author.	Case.	Affection.	Red cells.	Per cent hæmoglobin.
Osterspey[1]...	1	Cancer of the stomach.........	5,040,000	80
Osterspey....	2	Cancer of the liver and stomach	6,184,000	87
Osterspey....	3	Cancer of the gullet	8,280,000	48
Neubert[2]....	1	Cancer of the stomach.........	5,085,000	73
Neubert.....	2	Cancer of the liver	4,918,000	70
Reinert[3].....		Cancer of the stomach	6,200,000	77

[1] Dissert., Berlin, 1892.
[2] Inaug. Dissert., Dorpat, 1889.
[3] "Zählung d. Blutkörp.," Leipzig, 1891.

I wish to lay some stress upon this point, because it has been stated by some recent writers (*e.g.*, Grawitz: "Pathologie des Blutes," Berlin, 1896) that the red cells are almost always diminished in malignant disease.

The high counts in cancer of the gullet are obviously to be explained by the lack of liquid taken, the blood being greatly concentrated as in any other form of starvation.

That this increase is not invariably present (see Table XL., page 300) is doubtless because some œsophageal tumors permit the ingestion of liquid in normal amounts and of a certain amount of solids.

The highest counts in the Massachusetts Hospital series are in simple gastric cancer without any stenosis at either end of the organs (see Cases I., III., XVI., and XXI.), and the lowest count (1,632,000) was in a similar case just before death. Taking all the cases of cancer in this series together, *the average of the seventy-five cases at the time when treatment began was 4,140,-000 red cells per cubic millimetre.*

Hæmoglobin.

Bierfreund,[1] who has examined seventy-two cases with regard to their percentage of coloring matter, found that in relatively slow and long-standing cases it averaged 68.5 per cent, and in the worst cases 57.5 per cent. After the operation the hæmoglobin is of course lower owing to hemorrhage, and Bierfreund noticed that as a rule the hæmoglobin began to rise toward normal much later than after operations for non-malignant conditions—a week later on the average—*and that it never reached the point at which it was before the operation.*[2]

The following table from Bierfreund is of interest as illustrating these points. Cases were examined before and after operation, and the examinations were continued daily after the operation until the hæmoglobin began to rise

[1] Langenbeck's Archiv, vol. xli.

[2] This is all the more extraordinary because Bierfreund specially noted that even in patients who gained weight notably after the operation the hæmoglobin did not rise so high as it had been before operation; he watched them for months after it. Apparently the actual presence of the tumórs is not the only cause of the lack of corpuscle substance.

again. This occurred very late as compared with other operations.

Diagnosis.	Per cent hæmoglobin before operation.	Per cent hæmoglobin after operation.	Per cent loss.	Regeneration time.
Malignant tumor without complication.	68.5	53	15.5	23 days.
Very large or rapidly growing tumors.	56.6	38.4	18.2	27.8 days.
Tumors with "softening" or disturbances of function.	57.5	39.7	17.8	27 days.
Total, 72 cases.	Av., 60	Av., 42.8	17.2	Av., 25.9 days.

By "regeneration time" is meant the number of days elapsed after operation before the hæmoglobin *begins to rise.* After operations for other causes (non-malignant) the average regeneration time is fourteen to twenty days.

It is very important that these results of Bierfreund's should be tested. In Mikulicz's surgical clinic at Breslau all patients have their hæmoglobin tested regularly. In this country the surgical portion of the profession have not as yet taken hold of blood examination, and many questions about the blood in surgical affections remain unanswered.

Reinbach[1] examined 16 cases and found the hæmoglobin range between 18 to 70 per cent, with an average of 50 per cent.

Rieder's[2] cases average 53 per cent (sarcoma much lower—see below).

Laker[3] noticed the low hæmoglobin percentage in malignant tumors and thought it a help in excluding benign tumors or tuberculosis, in which the hæmoglobin is much less diminished.

In the 48 cases of malignant tumors in which I have notes of the hæmoglobin (see tables) the average is 54 per cent. Comparing this with the average count of red cells (4,140,000), we get a color index of .65, distinctly higher than the average of chlorotic cases, of which, however, the figures distinctly remind us. The highest cases of this series had 100 per cent and 90 per cent of hæmoglobin respectively, and the lowest 20 per cent

[1] Langenbeck's Archiv, 1893, p. 486.

[2] "Beiträge z. Kenntniss d. Leucocytosis," Leipzig, 1892 (Vogel).

[3] Wien. med. Woch., 1886, Nos. 18 and 19.

and 22 per cent; in these last two cases the color indexes were .36 and .58 respectively, not excessively low.

As the disease progresses, the red cells and hæmoglobin steadily go down (except in cancer of the gullet), and at the time of death 1,000,000 cells per cubic millimetre is not rare.

The color index always remains below 1. Compared to most other varieties of secondary anæmia (*e.g.*, those in tuberculosis or nephritis) a quantitative anæmia—that is, a loss of red cells as well as of hæmoglobin—is relatively more frequent. In general the degree of anæmia is parallel to the amount of cachexia, except when hemorrhage increases it (as in tumors of the stomach or uterus).

How far the anæmia may be due to actual destruction of cells by toxic (?) products of the tumors is doubtful. Grawitz found that the injection of extracts of cancerous tissues caused in rabbits a temporary dilution of the blood, so that the cells per cubic millimetre were diminished, and it may be that this plays some part in the causation of the low blood counts.

Qualitative Changes.

(*a*) *The average diameter of the red cells* is often diminished either (as in chlorosis) by a diminution of the size of nearly every corpuscle, or by a less general shrinkage, many cells being of normal size. The very large forms seen in pernicious anæmia are rare in the anæmia of malignant disease, and never, I think, reach the size of the giant forms seen in the former condition. Very small cells, on the other hand, are as common in advanced cases as in any other form of anæmia, except chlorosis. Deformities and degenerative changes are very common in well-marked cases.

According to Strauer, the *deformities* found in malignant disease are greater than those found in any form of tuberculosis, and this fact he thinks of value in diagnosis.

Degenerative changes are often well marked, but seldom, if ever, reach so extreme a condition as occurs in many cases of pernicious anæmia.

(*b*) *Nucleated red corpuscles* are the rule in all advanced cases, and in some that are not advanced. Malignant disease differs in this respect from tuberculosis and most other conditions involving secondary anæmia, in that the nucleated red cells may

appear even when there is no considerable loss of red cells (numerically) or even when the hæmoglobin is also normal (Schreiber).

As a rule the nucleated corpuscles are of the normoblast types (including small forms with dividing nuclei), but in very cachectic cases we may find megaloblasts as well—always, so far as I know, fewer in number than the normoblasts. This constitutes one of the points of distinction between pernicious anæmia and the severest types of secondary anæmia, such as occur in malignant disease. The megaloblasts, when present, are in the minority as compared with the normoblasts.

The characteristics of the blood changes in malignant disease, then, so far as concerns the red cells, are those of secondary anæmia, which at times attains the severest type—but only when cachexia is marked, or when hemorrhage complicates the disease.

The specific gravity follows in a general way the hæmoglobin percentage.

On the *white corpuscles* in malignant disease a great deal of interest has centred, and very conflicting reports have been published. As the effects of cancer and sarcoma seem to be somewhat different we will consider them separately.

1. The Leucocytes in Cancer.

(*a*) *Quantitative Changes.*

We should expect great differences in the blood of different cases if we consider what a wide range is included between the small, hard, slow-growing, curable cancer of the lip which may produce little or no impairment of the general health, and the "fulminating," rapidly growing cases with numerous metastases and profound prostration.

The former class of cases may show a blood normal in all respects, including a normal leucocyte count; while in the latter the blood may be so profoundly altered as to be confused with that of pernicious anæmia on the one hand, or with that of leukæmia on the other.

In a general way it may be said that the more "malignant" the cases the greater the changes in the blood.

The effect upon the leucocytes depends upon the following conditions:

1. The position of the tumor.

2. Its size, rapidity of growth, and the number, size, and position of its metastases.

3. The resisting power of the individual.

1. Position.—(*a*) Tumors of the gullet involving stricture but not extending to other tissues are often accompanied by a *diminution* of the leucocyte count, owing to the starvation which they produce. This is not true of all cases, as is shown in the accompanying tables, but when the leucocytes are *increased* there is usually an involvement of other organs as well.

(*b*) Cancers of the uterus and some of those of the stomach, by reason of the hemorrhage which they produce, are apt to be associated with a very high leucocyte count.

(*c*) Tumors of the thyroid and of the pancreas are said by some writers to cause a specially great leucocytosis. In my own experience, tumors of the kidney have shown very marked increase of white cells.

2. Size.—Other things being equal, the larger and more rapidly growing tumors show in most cases a greater leucocytosis than small, slow-growing ones.

Thus the cancers of the lip and of the pylorus, scirrhus of the breast or of the penis, show smaller counts than tumors of the liver, omentum, and kidney, which are apt to grow more rapidly. Metastases in the bone marrow are thought by some observers to give peculiar qualitative blood changes (see below).

In general, metastases, being a method of rapid growth, simply add to the leucocyte count.

These distinctions eliminate some of the apparent contradictions between the findings of different individuals who were simply describing cancers of different types. But even within a single type, there are very marked differences in different cases. For instance, Alexander[1] found the leucocyte count in cases of scirrhus of the breast to vary between 2,360 and 21,700. Similar differences have been reported in cancers of the stomach (*e.g.*, Schneider[2] finding leucocytosis in all of twelve cases, while

[1] Alexander: Thèse de Paris, 1887.

[2] Inaug. Dissert., Berlin, 1888.

Osterspey[1] in another series of twelve cases found leucocytosis in only two).

3. *Resisting Power.*—Possibly a part of these differences is to be explained by differences in the resisting power of the individual. But if this is so, we cannot measure the endurance of a given patient by his general health. As in the Civil War the pale, city-bred men outlasted the healthy farmers, so here the tumor's rapidity of growth seems often to be greatest in the most vigorous young individuals, while dried-up old women will resist its advance for a longer period.

We come now to the conditions to be found in particular types of cancerous growth.

Surprisingly little work has been done on the blood in malignant disease, such cases usually being under the charge of surgeons who rarely value such investigations. Except for scattered counts here and there, all our knowledge of the corpuscles rests on the work of Hayem and Alexander in France, and Rieder, v. Limbeck, Pée, Sadler, Reinbach, Osterspey, Grawitz, Strauer, Schneyer, and Schneider in Germany.

CANCER OF THE BREAST.

Most of our data come from Hayem[2] and his pupil Alexander.[3]

1. *Scirrhus Growths.*—Number of cases, 14. Average leucocyte count, 11,400. Highest count, 21,700; lowest, 2,360—the last is somewhat doubtful as to diagnosis; except for this case, which was in a very old, dried-up woman, the lowest count was 7,400.

In 10 out of the 14 cases, the count was over 10,000. In the 3 cases seen by the writer 2 showed no leucocytosis, 1 a considerable leucocytosis.

2. *Medullary (Encephaloid) Growths.*—Three cases, all over 10,000—average 11,300.

[1] Inaug. Dissert., Berlin, 1892.

[2] Hayem: "Du Sang," Paris, 1889, p. 947.

[3] G. Alexander: "De la Leucocytosis dans les Cancers," Paris Thesis, 1887.

Effects of Operation.

The following figures from Hayem are also of interest:

CASE I.—Scirrhus of the Breast.

Before operation	21,700	
Five weeks after operation (wound not quite healed)	10,000	
Wound completely healed	6,200	
Seven months after operation	8,990	(beginning to rise again)

The growth recurred some months later and leucocytosis was again present.

CASE II.—Scirrhus of the Breast.

	First count.	Second count.
Before operation	11,500	11,450
After operation	8,500	6,200

CASE III.—Scirrhus of the Breast.

	First count.	Second count.
Before operation	11,000	12,400
After operation	8,400	

CASE IV.—Scirrhus of the Breast.

Before operation	7,400
After operation	1,300

CASE V.—Medullary Cancer of the Breast.

Before operation	10,000
After operation	9,000

Hayem considers that by watching the leucocyte count we can predict the coming of a recurrence before any physical signs are present. This he did in Case I. of the series just given.

I have seen no confirmation or refutation of this statement. It is one of the many points to which the attention of surgeons should be directed.

CANCER OF THE STOMACH.

Here we have a much larger body of data to judge from. Thus:

Hayem[1] in 12 cases found leucocytosis present in 5, absent in 7.

[1] "Du Sang," Paris, 1889, p. 948.

Schneider[1] in 12 cases found leucocytosis in 12 (all).

Schneyer[2] in 18 cases found leucocytosis in 4, and these 4 all under 11,000.

Osterspey[3] in 12 cases found leucocytosis in 5.

Rieder[3] in 6 cases found leucocytosis in 3.

Sadler[4] in 13 cases found leucocytosis in 2, and in both there were complications (abscess of liver, perforation of gullet with gangrene) to which the leucocytosis might be due.

Reinbach[5] in 4 cases found leucocytosis in 2.

Reinert[6] in 2 cases found leucocytosis in 2.

Laache[7] in 5 cases found leucocytosis in none.[8]

Despite these facts we have the record of a certain number of single cases in which the leucocytosis has been enormous. For instance, Welch in "Pepper's System of Medicine" mentioned a case in which the ratio of white to red cells was 1:25 (normally 1:750±). Eisenlohr's[9] case showed 1 white to 50 red and Potain's[10] case showed 1 white to 48 red cells.

The Massachusetts Hospital series of 46 cases showed leucocytes in 15 cases and none in 31 (see Tables XXXIX., A, B). Out of those showing leucocytosis 6 were under 12,500, that is the leucocytes were but slightly increased, leaving only 9 out of 45 (or twenty per cent) in which the leucocytosis was very marked. Among these 9, the highest counts were 40,000 and 39,000, and the highest ratio 1:62.

In this series I have excluded all cases in which there was evidence of metastasis in other organs; this means excluding 7 cases, 6 of which showed leucocytosis, and helps to account for the low average leucocyte count in the other 46 cases.

In over three-fourths of these cases the diagnosis was made certain either by operation or by autopsy; all the others showed

[1] Inaug. Dissert., Berlin, 1888.

[2] Inaug. Dissert., Berlin, 1892.

[3] *Loc. cit.*

[4] Original-Mittheilungen aus der Klinik v. Jaksch, 1891.

[5] Langenbeck's Archiv, 1893, p. 486.

[6] *Loc. cit.*

[7] "Die Anämie," Christiania, 1883.

[8] Apparently, since he draws attention to the fact that there is leucocytosis in a case of cancer of the uterus.

[9] Deut. Arch. f. klin. Med., 1877, vol. xx.

[10] Gaz. des Hôp., 1888, No. 57.

either a palpable tumor in old cachectic patients with pain and vomiting, or other equally clear evidence for the diagnosis. Doubtful cases have been excluded. As will be seen by the table, in some of the cases the counts were verified by repeated examinations, while in others only a single count—that made when the patient entered the hospital—was recorded.

As a rule, the high leucocyte counts were in the more cachectic cases; but this does not always hold. Cases 10, 11, and 28 in Table XXXIX., A, were very cachectic but showed no leucocytosis.

The position of the tumor in one or another part of the stomach seemed to have no connection with the number of leucocytes.

On the whole, leucocytosis is relatively infrequent in cancer of the stomach, occurring in only about one-third of the early cases. As the disease progresses we may get a leucocytosis, particularly in case its growth is *rapid* and metastases are frequent and numerous; but some cases, particularly those in which the tumor is small and grows slowly, may run their entire course without any leucocytosis being present. In this respect they are like the majority of small, slow-growing cancers in other parts of the body (see below).

Hemorrhage or perforation is of course accompanied by an increase in the number of white cells—in fact the highest count in the present series (105,600) occurred in a case in which a cancer of the stomach with metastases in the liver perforated into the peritoneal cavity and started a virulent, quickly fatal peritonitis.

DIGESTION LEUCOCYTOSIS IN CANCER OF THE STOMACH.

A considerable body of statistics has accumulated to show that in the great majority of cases of gastric cancer the leucocytosis of digestion (see above, page 84) does not occur. R. Müller[1] noticed this fact in 5 cases of cancer of the stomach. Schneyer[2] in 18 cases found it invariably absent, while in 3 cases of benign stenosis of the pylorus a considerable digestion leucocytosis appeared, as was also the case in 7 out of 8 cases of ulcer of the stomach.

[1] Prag. med. Woch., 1890, No. 17.
[2] Zeit. f. klin. Med., 1895, p. 475.

He found both incipient and advanced cases to be similarly affected. In 5 of his cases and in some of Müller's HCl was present in the gastric contents, so that the absence of digestion leucocytosis was not due to absence of HCl.

Hartung (*Wiener klin. Woch.*, p. 697, 1895) in a series of 10 cases (mostly advanced) found no digestion leucocytosis.

Capps[1] in 14 cases examined at the Massachusetts General Hospital found a digestion leucocytosis in 2, the increase being respectively 4,100 and 3,850 cells over the count before the beginning of digestion. In the other 12 cases there was no increase after a large proteid meal.

Two cases of ulcer of the stomach showed marked increase, as did several cases of hyperacidity and other gastric disorders (see Diseases of the Stomach, page 241).

CANCER OF THE STOMACH WITH METASTASES.

Most writers have not separated the cases with metastasis from those without it. A glance at the seven cases of Table XXXIX., C, shows that with one exception leucocytosis was present throughout most of the disease.

TABLE XXXIX., C.—CANCER OF THE STOMACH WITH METASTASES.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	48	M.	4,228,000	5,000	70	January 23d. Stomach and liver.
				6,200	....	January 28th, mealtime.
				7,300	....	January 28th, three hours later.
2	41	M.	4,272,000	10,000	57	Stomach, liver, and glands.
3	38	M.	5,432,000	10,190	52	January 6th. Stomach and liver.
				13,653	....	January 12th.
						January 22d, died.
4	66	M.	....	7,000	70	February 14th, no cachexia.
			5,168,030	14,400	62	March 6th, liver involved.
				19,600	....	March 12th.
				21,640	....	March 17th, cachectic.
5	Adult.	M.	3,352,000	16,000	....	Stomach, liver, and spleen.
6	54	M.	4,160,000	24,000	60	Stomach and liver.
				24,200		
				22,500		
7	47	M.	....	34,350	....	November 7th, cancer of stomach and liver.
				30,600	....	November 11th.
				105,600 !	....	November 14th, perforation peritonitis.

[1] Boston Med. and Surg. Journal, 1896.

CANCER OF THE GULLET.

Most authors are agreed that *no increase*—in fact usually a decrease—of white cells is the rule in this disease. Thus Rieder found 6,900 in one case; Osterspey's two cases showed no leucocytosis, and Escherich and Pée found similar results.[1] This is probably due to the fact that the position of the tumor, by causing starvation, tends to lower the leucocytes, while it belongs to the class of small, slow-growing cancers which do not as a rule tend to produce leucocytosis.

Nevertheless, two of the five cases in the Massachusetts Hospital series (see Table XL.) *did* have leucocytosis, perhaps owing to some metastasis or complication. There was no autopsy in either.

TABLE XL.—CANCER OF THE GULLET.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	58	M.	5,488,000	6,800	100 (!)	May 18th.
				6,800	....	May 11th.
2	56	M.	4,920,000	8,725	72	
3	51	M.	2,824,000	7,600	50	Before food.
				11,500	....	Four hours after.
4	67	M.	4,604,000	16,400	60	One and one-half hours after food.
5	38	F.	4,560,000	20,600	50	

CANCER OF THE LIVER.

(See Table XLI.)

Out of fourteen cases, leucocytosis was present in eight—a larger proportion than in gastric cancer. The cases were not all primary in the liver or bile ducts, but none originated in the stomach, and in all the greater part of the growth was in the liver itself.

The comparatively great diminution in the red corpuscles will be noted in the Table XLI. The condition both of red and white cells is doubtless due to the rapid growth of tumors of the

[1] Reinbach's two cases showed a diminution in the polymorphonuclear cells, which in all probability means a normal or diminished leucocyte count.

liver as compared, *e.g.*, with those of the stomach or lip (see below).

TABLE XLI.—CANCER OF THE LIVER.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	55	M.	4,170,000	5,000	....	Bile ducts=starting-point. Autopsy.
2	61	M.	3,894,000	5,200	52	
3	59	M.	4,570,000	8,000	....	Operated.
4	72	M.	4,100,000	9,000		
5	44	F.	4,952,000	7,800	69	January 4th, 1896. Autopsy.
			3,784,000	19,700	68	February 12th, 1896.
6	54	M.	4,072,000	9,800		Differential count of 1,000 cells: Poly., 82.4 per cent; small lymphocytes, 8.5; large lymphocytes, 8.1; old lymphocytes, 1.
7	50	M.	3,900,000	10,800	....	Primary in bile ducts. Autopsy.
8	?	M.	4,108,000	9,970	45	January 1, 1896.
				11,200	....	January 3d, 1896. Autopsy.
9	43	M.	4,160,000	14,100	?	July 17th.
						July 19th. Autopsy
10	64	M.	2,768,000	15,800	45	May 6th.
			2,880,000	21,900	....	May 24th.
				1,580	45	May 28th.
			2,928,000	11,700	....	June 8th.
11	35	M.	3,800,000	9,800	....	November 3d.
				22,000	....	November 5th.
						November 6th. Differential count of 500 cells: Poly., 92 per cent; lymphocytes, 8. Autopsy.
12	48	F.	2,900,000	17,500	48	Differential count of 500 cells: Poly., 92 per cent; lymphocytes, 5.8; eosinophiles, .2; myelocytes, 2. Autopsy.
13	Adult.	M.	4,408,000	25,500	70	
14	50	M.	4,544,000	35,600	....	November 29th, 1895.
				36,400	....	December 10th, 1896.
			3,186,000	23,000	....	January 15th. 1896.
			4,056,000	28,800	....	February 16th, 1896. Autopsy.

CANCER OF THE INTESTINE.

Here the counts range both high and low.

Hayem[1] found cancer of the rectum to show only 9,500 leucocytes. Reinbach[2] found in three cases of cancer of the rectum moderate leucocytosis.[3] Only two of the seven cases in our series (see Table XLII.) showed leucocytosis and in one of these there was a complicating pylephlebitis which probably raised the count.

The red cells show little change.

[1] *Loc. cit.*

[2] *Loc. cit.*

[3] Apparently—that is, the percentage of adult cells was increased. He did not count the leucocytes as a whole.

TABLE XLII.—CANCER OF THE INTESTINE.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	56	M.	4,408,000	12,700	60	Cancer of duodenal papilla with pylephlebitis. Autopsy.
2	41	F.	5,560,000	5,800	45	Cancer of cæcum. Operated successfully.
3	31	M.	4,921,000	8,800	....	Cancer of hepatic flexure. Operated.
4	33	M.	4,868,000	5,800	83	Cancer of colon. Operated.
5	59	F.	4,800,000	5,500	88	Cancer of cæcum. Autopsy.
6	66	M.	4,268,000	7,150	78	Cancer of intestine (where ?).
7	50	F.	5,416,000	12,000	....	Cancer of rectum.

CANCER OF OMENTUM AND ABDOMINAL ORGANS GENERALLY.

The seven cases seen at the Massachusetts General Hospital in which cancerous tissue was pretty generally distributed through the abdominal organs, all showed leucocytosis with one exception, the counts ranging high (see Table XLIII., A and B).

TABLE XLIII., A.—CANCER OF OMENTUM AND ABDOMINAL ORGANS GENERALLY.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	50	F.	....	Greatly increased	Markedly diminished.	Primary in pancreas. Differential count of 400 cells: Poly., 84.5 per cent; small lymphocytes, 8; large lymphocytes, 5; eosinophiles, 2.5. Autopsy.
2	26	M.	....	9,000		
3	65	M.	....	11,700		
4	Adult.	M.	3,772,000	13,700	....	Autopsy.
5	Adult.	F.	5,500,000	26,200	....	Autopsy.
6	45	F.	....	27,400	....	Question of aneurism. Autopsy.
7	Adult.	M.	....	Greatly increased	Markedly diminished.	Differential count of 500 cells: Poly., 80 per cent; lymphocytes, 20.

CANCER OF THE KIDNEY.

Of four cases which I have examined (see Table XLIII., B) *all* showed very large leucocyte counts—viz., 27,000, 28,500, 43,-100, 82,000, and 91,000, an average of 54,000. In two of these cases, however, the tumors may have been sarcomata, as no microscopic examination was made. Most of the cases had

fever, chills, and signs of inflammation, which may account for part of the leucocytosis.

TABLE XLIII., B.—CANCER OF KIDNEY.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	2	F.	3,756,000	27,000	....	Differential count of 500 cells: Poly., 66 per cent; lymphocytes, 29.5; eosinophiles, [illegible]; myelocytes, 2.5; normoblasts, 24; megaloblasts, 2. Autopsy.
2	57	F.	5,200,000	28,500	....	Supposed leukæmia. Differential couut of 500 cells: Poly., 81.8 per cent; small lymphocytes, 12; large, lymphocytes, 4.2; eosinophiles, 2. Autopsy.
3	49	F.	3,360,000	43,100	....	Supposed leukæmia. Differential count of 1,000 cells: Poly., 92.9 per cent; lymphocytes, 6.2; myelocytes, .9; normoblasts, 2; megaloblasts, 1. Autopsy.
4	50	F.	4,111,000	82,000	....	July 8th.
			2,780,000	91,000	....	Poly., 98 per cent; lymphocytes, 2.

Von Limbeck's[1] case mounted steadily from 18,514 to 80,541.

CANCER OF THE UTERUS.

In six cases Hayem[2] found no increase—the counts ranging from 4,575 to 9,500 with an average of 7,800.

Rieder,[3] on the other hand, in a single case found 30,800, and the three cases counted at the Massachusetts Hospital showed respectively 19,400, 22,250, and 34,900 (see Tables XLIV., A and B).

There is need of more data on this subject.

TABLE XLIV., A.—CANCER OF THE UTERUS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	48	F.	2,696,030	19,400	20	October 26th.
			3,232,000	30,700	27	October 28th.
2	51	F.	....	34,900	....	Differential count of 1,000 cells: Poly., 88 per cent; small lymphocytes, 11.7; eosinophiles, .2; myelocytes, .1. Two normoblasts.
3	31	F.	2,889,680	22,250		

[1] *Loc. cit.* [2] *Loc. cit.* [3] *Loc. cit.*

TABLE XLIV., B.—CANCER OF THE OVARY.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	36	F.	4,500,000	25,000	62	Operation.
2	....	F.	3,248,000	32,800	....	Operation.
				CANCER OF THE PROSTATE.		
1	45	M.	....	10,200		
				CANCER OF THE LIP.		
1	51	M.	7,600,000	6,300		
				CANCER OF THE BREAST.		
1	31	F.	6,000,000	8,000		
2	?	F.	......	Not increased	....	Differential count of 600 cells: Poly., 72.4 per cent; lymphocytes, 25.4; eosinophiles, 2.2.
3	?	F.	....	Marked increase.	....	Differential count of 400 cells: Poly., 89 per cent; lymphocytes, 11.
				CANCER OF THE NECK.		
1	42	M.	....	Marked increase.	....	Poly., 88.5 per cent.

Cancer of the lip has apparently been neglected so far as blood examination is concerned. Hayem, Rieder, and Reinbach give but one case each, the counts being respectively 7,000, 11,-600, and "not increased." In a single case at the Massachusetts Hospital I found 6,300.

The following scattered counts may be added: Cancer of tongue, 7,000 (Hayem); cancer of scrotum, 6,700 (Hayem); cancer of navel, 7,100 (Hayem); cancer of larynx, 7,200 (Hayem), 16,000 (Reinbach); cancer of ovary, 25,000 (Massachusetts Hospital) and "no increase" (Reinbach); cancer of neck, 20,000 (Massachusetts Hospital) and "no increase" (Reinbach); cancer of pancreas: Hayem, 2 cases—9,400 and 9,900; Schneider, 1 case—12,000; cancer of vagina, 9,800 (Rieder); cancer of penis, 7,000 (Hayem); cancer of thyroid, 70,000 (Hayem) (a very rapidly growing tumor); cancer of mediastinum, "marked increase" (Reinbach); cancer of prostate,[1] 10,200.

[1] Braun (Wien. med. Woch., 1896, p. 582) mentions a cancer of the prostate in whichthe leucocytosis instead of being made up mostly by the adult leucocytes, was associated with a large increase of the small lymphocytes together with numerous eosinophilic myelocytes.

Qualitative Changes in the Leucocytes.

1. Whenever *leucocytosis* is present we find, as in most pathological leucocytoses, a marked increase of the adult, at the expense of the young, cells.

Reinbach found in 8 cases with leucocytosis 89 per cent in 2 cases and 87, 86, 83, 81, 80, and 77 per cent in others. In the Massachusetts General Hospital series the following percentages occurred: When no leucocytosis was present 62.5 and 62 per cent. With leucocytosis, 96, 98, 92, 86, 84 per cent, etc. (See Tables XXXIX., XLI., XLIII., XLIV.)

2. *Eosinophiles* are not always notably decreased (as they are in many other leucocytoses) nor are they increased except when bone metastasis occurs (see below). In Reinbach's 16 cases the average percentage was 2 + per cent. In the Massachusetts Hospital cases the average was 1.2 per cent, but in 4 of the 14 cases in which differential counts were made, no eosinophiles were seen.

3. *Myelocytes.*—Perhaps more commonly than in other conditions except leukæmia and pernicious anæmia, we find in malignant disease small percentages of myelocytes, as the following cases show:

CASE I.—Extensive abdominal cancer; great cachexia. Six hundred cells showed:

"Polynuclear neutrophiles"	89.4	per cent.
Lymphocytes	10.	"
Eosinophiles	.1	"
Myelocytes (3 in 600 cells)	.5	"

CASE II.—Cancer of uterus; marked cachexia and leucocytosis. One thousand cells showed:

"Polynuclear neutrophiles"	82.3	per cent.
Lymphocytes	17.3	"
Myelocytes (4 in 1,000 cells)	.4	"

CASE III.—Cancer of uterus; died two days later. Red corpuscles, 7,000,000; white, 62,000. Considerable stasis helps to explain the count. Differential count of 500 cells showed:

"Polynuclear neutrophiles"	93	per cent.
Lymphocytes	6	"
Eosinophiles	0	"
Myelocytes (5 out of 500)	1	"

CASE IV.—Cancer of liver, jaundice and cachexia; died soon after. Differential count of 500 cells showed:

"Polynuclear neutrophiles"	92.	per cent.
Lymphocytes	6.	"
Small myelocytes	1.2	"
Large myelocytes (4 in 500)	.8	"

CASE V.—Cancer of abdomen; cachectic. Differential count of 1,000 cells showed:

"Polynuclear neutrophiles"	82.	per cent.
Lymphocytes	16.6	"
Eosinophiles	1.	"
Myelocytes (4 in 1,000)	4.	"

CASE VI.—Cancer of stomach, liver, etc., with perforated stomach; cachexia. Leucocytes, 105,000. Fifteen hundred cells showed:

"Polynuclear neutrophiles"	90.7	per cent.
Lymphocytes	4.8	"
Eosinophiles	.2	"
Myelocytes (68 in 1,500)	4.3	"

CASE VII.—Cancer of uterus; cachexia. In 1,000 cells there were:

"Polynuclear neutrophiles"	88.	per cent.
Lymphocytes	11.7	"
Eosinophiles	.2	"
Myelocytes	.1	"

CASE VIII.—Cancer of kidney; great cachexia. In 1,000 cells there were:

"Polynuclear neutrophiles"	92.9	per cent.
Lymphocytes	6.2	"
Myelocytes	.9	"

CASE IX.—Cancer of kidney; great cachexia. Leucocytes, 27,000. Five hundred cells showed:

"Polynuclear neutrophiles"	66.	per cent.
Lymphocytes	29.5	"
Eosinophiles	2.	"
Myelocytes	2.5	"

CASE X.—Cancer of liver. Five hundred cells showed:

"Polynuclear neutrophiles"	92.	per cent.
Lymphocytes	5.8	"
Eosinophiles	.2	"
Myelocytes	2.	"

Whether there is any reason to suspect bone metastasis in these cases I do not know. There were no examinations of the bones made post mortem.

Epstein (*Wiener med. Presse,* December, 1894) in a case of cancer with metastatic bone nodules noticed large numbers of nucleated corpuscles (normoblasts and megaloblasts) and myelocytes.

SARCOMA.

In general the effects of sarcoma are like those of cancer, but *worse.* Great anæmia and higher leucocyte counts are the rule. The literature of the subject is rather scanty.

Red Cells.—Hayem in a case of osteosarcoma counted the red cells at 663,400 per cubic millimetre.

Laker[1] describes an "abdominal cystosarcoma" in which two counts of red cells showed 2,800,000 and 2,500,000.

Von Limbeck[2] in 1 case found 1,118,000, and in another 2,240,000. Both were osteosarcomata.

Sadler[3] in 3 cases found 2,710,000, 3,637,000, 4,500,000.

Rieder[4] in 3 cases (all osteosarcomata) found 1,846,160, 3,770,000, and 3,995,000.

The Massachusetts Hospital blood counts include 12 cases in which the red cells were counted (see Table XLV., A and B), the average being 4,400,000, not nearly so low as that recorded by other observers; still low counts occurred (2,706,000, 2,637,000, 3,842,000).

The qualitative changes in the red cells consist (as in cancer) of the "degenerative" changes (deformities in size and shape, englobular changes) present in marked cases, and the presence of nucleated corpuscles, when cachexia is marked.

[1] Wien. med. Woch., 1886, p. 926.
[2] *Loc. cit.*, p. 343.
[3] *Loc. cit.*, pp. 38, 39.
[4] *Loc. cit.*, pp. 98, 100.

TABLE XLV., A.—SARCOMA WITH LEUCOCYTOSIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	21	F.	2,706,000	56,000	....	Sarcoma of kidney. Autopsy.
2	35	F.	4,560,000	17,000	65	Melanotic sarcoma all abdominal organs (bone metastasis ?). November 30th, 1895. Differential count of 600 cells: Poly., 71 per cent; small lymphocytes, 11; large lymphocytes, 5.2; eosinophiles, 12.4 (!); myelocytes, .4.
				23,900	....	December 7th.
				33,400	....	December 13th.
				37,900	....	December 19th.
				41,200	....	
				33,000	....	December 22d.
				36,000	....	December 26th.
				40,200	....	January 14th.
				55,400	....	January 28th.
3	46	M.	4,700,000	16,000	....	Sarcoma of abdominal organs.
				19,000	....	Three days later. Autopsy.
4	32	M.	2,630,000	24,000	50	General sarcomatosis.
			2,900,000	21,000	....	One week later. Autopsy.
5	24	M.	4,352,000	13,600	....	Sarcoma of kidney.
6	41	M.	3,842,000	61,100	55	Sarcoma of lung, etc. Autopsy.
7	68	F.	6,200,000	16,000		Sarcomatosis.
8	48	M.	....	Marked increase.	....	Differential count of 700 cells: Poly., 70 per cent; lymphocytes, 22; eosinophiles, 1; myelocytes, 7. Sarcomatosis.
9	57	M.	4,180,000	13,000	47	Melanotic sarcoma of abdominal organs.
				16,250	....	One week later.
				15,180		
10	Adult.	M.	. ...	18,000	....	Sarcoma of abdominal organs.
11	....	....	....	Great increase.	....	Osteosarcoma (thigh). Differential count of 500 cells: Poly., 74 per cent; small lymphocytes, 19; large lymphocytes, 6; eosinophiles, 1.
12	....	....	....	Great increase.	....	Sarcoma of abdominal organs. Differential count of 800 cells: Poly., 84 per cent.; lymphocytes, 15.5; eosinophiles, .5.
13	....	....	....	13,200	....	Sarcoma of abdominal wall.

TABLE XLV., B.—SARCOMA WITHOUT LEUCOCYTOSIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	29	M.	5,280,000	8,200	......	Sarcoma of testicle.
2	37	F.	4,980,000	9,000	78	Sarcoma of ovary.
3	?	M.	4,946,000	9,000	....	Osteosarcoma of shoulder.
4	24	M.	4,952,000	6,000	....	Small recurrent sarcoma of groin.

Small tumors are often without any effect on the blood (see Table XLV., B). According to v. Limbeck[1] this is oftener true than in cancer.

Hæmoglobin.—Reinbach's[2] 20 cases ranged between 23 and 75 per cent, averaging 52 per cent.

[1] *Loc. cit.* [2] *Loc. cit.*

Bierfreund[1] in 29 cases found variations between 40 and 75 per cent.

Von Limbeck's 2 cases had 28 and 48 per cent respectively.

Rieder's[2] 4 cases showed at the beginning of treatment 29, 56, 57, and 65 per cent respectively, but in 1 case the hæmoglobin went down gradually while under observation until it reached 6 per cent (!), the lowest point, Rieder says, that he has ever seen in any disease.

Sadler's[3] cases showed 33, 45, and 78 per cent.

In the 5 cases of Table XLV. in which this point was noted, the average is 58 per cent.

On the whole, the coloring matter seems to be more diminished than in most cases of cancer.

Leucocytes.—The following tables, slightly modified from v. Limbeck, show the important points.

For other sarcomata, see Tables XLV., A and B.

On the whole, leucocytosis appears to be more constant and of greater extent in sarcoma than in cancer.

No.	Observer.	Diagnosis.	Count.
1	Hayem.	Osteosarcoma.	11,250
2	Alexander.	"	52,700
3	"	"	16,430
4	"	"	16,275
	"	"	17,050
5	"	"	15,900
	"	"	15,570
6	"	"	13,020
7	"	"	10,950
	"	"	12,090
8	"	"	11,248
9	Rieder.	"	12,700
	"	"	10,900
10	"	"	9,100
11	"	"	8,000
12	v. Limbeck.	"	32,000
	"	"	26,800
13	Reinbach.	"	20,000
14	"	"	13,000
15	Massachusetts Hospital.	"	21,000
16	" "	"	9,000
		Average,	17,000 ±

[1] *Loc. cit.* [2] *Loc. cit.* [3] *Loc. cit.*

No.	Observer.	Diagnosis.	Count.
1	Hayem.	Lymphosarcoma.	11,700
2	Alexander.	"	19,910
3	"	"	19,530
4	"	"	11,696
5	"	"	11,470
6	"	"	10,540
7	v. Limbeck.	"	55,100
8	"	"	38,000
9	"	"	10,800
10	Sadler.	"	33,248
11	"	"	19,299
12	"	"	9,044
		Average,	20,000 +

No.	Observer.	Diagnosis.	Count.
1	Rieder.	Melanosarcoma.	41,600
2	"	"	28,500
3	"	"	22,300
4	Reinbach.	"	25,000
5	"	"	8,000
6	Massachusetts Hospital.	"	37,900
7	" "	"	13,000
		Average,	25,100 +

Qualitative Changes.

1. The increase of adult leucocytes which we find in most forms of leucocytosis is not always present in sarcoma[1] and seems to be less frequent than in cancer (see Cases II., VIII., and XI., Table XLV.).

As in cancer, it may be present when no increase in the total leucocyte is to be found, and may be the only indication of any disease in the organism.

2. A few cases are on record in which a large percentage of *eosinophiles* has been present.

Reinbach found 48 per cent of eosinophiles in a case of sarcoma of the neck with sloughing and ulcerative endocarditis, the

[1] Palma (Deut. Med. Woch., 1892) reports lymphocytosis in sarcoma.

percentage continuing over 40 for several weeks.[1] Autopsy showed sarcomatous nodules in the bone marrow. In another case, a tumor of the abdomen, the eosinophiles were 10.5 per cent, and in two others 8 per cent.

A case of apparent sarcoma of the abdominal organs (no autopsy) at the Massachusetts General Hospital in January, 1896, had 12.4 per cent of eosinophiles.

Such cases should certainly make us think of bone metastases, and Neusser speaks of osteosarcomata as being accompanied by eosinophilia, but the evidence is as yet fragmentary.

3. *Myelocytes.*—Reinbach's case just described had a low percentage of myelocytes.

The following cases illustrate the same point:

Case I. is a case of sarcomatosis in a man in whom sarcomatous nodules were distributed all over the internal organs and in the skin. A differential count of 700 white cells showed in his case:

Typical myelocytes (over 15μ)	2	per cent.
Small myelocytes (under 15μ)	5	"
Lymphocytes	22	"
"Polynuclear neutrophiles"	70	"
Eosinophiles	1	"

The autopsy showed no special lesions in the spleen, glands, or bone marrow, except those due to the sarcomatous nodules.

[1] The full counts are as follows:

April 4th, 1892.		May 20th, 1892.	
Red cells	5,396,000	Red cells	4,512,000
White cells	120,000 (!)	White cells	52,000
Hæmoglobin	60 per cent.	Hæmoglobin	55 per cent.

DIFFERENTIAL COUNTS.

	April 4th.	May 1st.	May 20th.	May 26th.
	Per cent.	Per cent.	Per cent.	Per cent.
Poly. neut.	48	51	55 +	51 +
Eosinophiles	48	46	42	44 +
Lymphocytes	2.7	2.32	1.5	3.2
Myelocytes	1	.68	.64	.8

CASE II.—Sarcoma of abdominal wall. Differential count of 800 cells showed:

"Polynuclear neutrophiles"	84.	per cent.
Lymphocytes	10.5	"
Large lymphocytes	5.	"
Eosinophiles	.2	"
Myelocytes	.3	"

CASE III. (No. 2, Table XLV., A).—Six hundred cells contained:

"Polynuclear neutrophiles"	71.	per cent.
Lymphocytes	16.2	"
Eosinophiles	12.4	"
Myelocytes	.4	"

Summary of Blood Changes in Malignant Disease.

1. Small, slow-growing tumors and the early stages of all tumors may have no effect on the blood appreciable by our present methods of examination.

2. In advanced cases the red corpuscles often become thin, light, and pale, and finally their number may be greatly decreased, the counts running sometimes as low as in pernicious anæmia. In this respect, as in others, sarcomata seem to injure the blood more than cancers.

3. The color index is always below 1, but is rarely as low as we find it in severe chlorosis.

4. Normoblasts and megaloblasts (the latter being in the minority) may occur, the former even in the absence of severe anæmia. Deformities in size and shape are common.

5. Leucocytosis is present in the cachectic end-stages of many cases, but is frequently absent in small tumors of slow growth and without metastases. The adult cells are often relatively increased.

6. Fibrin is not increased.

Diagnostic Value.

1. When we are dealing with an obscure, deep-seated disease, if hemorrhage is excluded, the presence of persistent leucocytosis suggests suppuration or malignant disease (rather than tuberculosis or syphilis, for example), and excludes any simply

functional or hysterical affection. The *absence* of leucocytosis, however, does not exclude malignant disease, though it makes suppuration very unlikely.

2. Between malignant disease and suppuration—if the other signs and symptoms do not decide—there may be nothing in the blood to decide. In decided pyæmia we may get pyogenic cocci from the blood by culture, but a negative result would not exclude the suppurating focus.

The *absence* of any increase of fibrin in the blood speaks against suppuration, and therefore in favor of malignant disease; but the presence of increased fibrin network is not decisive either way, as it may be met with in connection with neoplasms, though more common in suppuration.

3. Between malignant disease and hemorrhage—a marked anæmia favors the latter, provided the case is a recent one; for the anæmia of malignant disease is comparatively slow to develop. The leucocytes give no help.

4. Between cancer and ulcer of the stomach, if there has been no recent hemorrhage, leucocytosis favors cancer; but its *absence* is of no weight either way.

The hæmoglobin is said to decrease steadily in cancer, while in ulcer it tends to return toward normal after the cessation of hemorrhage.

The presence and persistence of digestion leucocytosis speak against cancer, and its absence in favor of cancer. It must be remembered, however, that any variety of *catarrh* or *dilatation* (should such be present) can also prevent digestion leucocytosis, and that the latter is not invariably present even in health.

5. Between cancer of the liver or bile ducts on the one hand and *simple* gall-stone colic or gall-stone obstruction, the presence of leucocytosis favors cancer. As usual, however, its absence does not exclude cancer, and we must bear in mind that gall stones *with cholangitis* may raise the leucocyte count as much as cancer. Simple cysts or echinococcus cysts cause no leucocytosis, nor does syphilis of the liver.

6. The appearance in the blood of large numbers of eosinophiles, myelocytes, and nucleated corpuscles during the course of a malignant disease points to a bone metastasis.

7. When a leucocytosis which has disappeared after removal

of a neoplasm reappears, we may expect recurrence of the growth shortly.

8. A steadily increasing leucocytosis in a case of malignant disease points to a rapidly growing tumor or to the occurrence of metastasis.

9. Between malignant disease and pernicious anæmia the diagnosis rests on the following points:

I. Color index low in malignant, apt to be high in pernicious anæmia.

II. Leucocytes often increased in malignant, diminished in pernicious anæmia.

III. Lymphocytes often decreased in malignant, increased in pernicious anæmia.

IV. Average size of red cells often decreased in malignant, and often increased in pernicious anæmia.

V. If nucleated red corpuscles are present the normoblasts are in a majority in malignant disease, and in a minority in pernicious anæmia.

10. The presence of leucocytosis is against the benignness of any tumor.

11. When no actual increase of leucocytes is present, an increased percentage of the adult variety among those present may have the same significance as a leucocytosis.

CHAPTER XI.

BLOOD PARASITES AND INTESTINAL PARASITES.

Examination for the Plasmodium Malariæ and its Products.

I. *Time for Examination.*—It is often stated that the organism is most easily found during the chill. But this is not the writer's experience. During a chill it is often difficult and sometimes impossible to find the organisms. Eight hours before or after a chill is a much more favorable time, although parasites have been found as late as forty-eight hours after the last chill. During the chill many organisms retire to the internal organs.

The number of organisms varies a great deal. In some cases they are present in every field of a one-twelfth immersion lens, while in others we may find only one after an hour or more of patient search. In the majority of the cases occurring near Boston, it needs but a few minutes' search to find them if the blood be taken within twelve hours before or after a chill, and provided no quinine has been lately given. Occasionally in mild cases the organisms are very scanty; and it may be almost impossible to find any. The quartan and æstivo-autumnal forms of malaria are so rare in New England that I shall not attempt to describe the parasites found in them, but shall confine myself mostly to the parasites of common tertian and double tertian fevers with which I am personally familiar.

II. *Method of Examination.*—A slide of fresh blood is prepared as above described (pages 3–7) and examined with a one-twelfth immersion lens.[1] Lower powers should not be used, although in skilful hands they are often sufficient. Portions of the slide in which the corpuscles do not overlie each other should be chosen for examination. As we pass the slide along beneath the lens it is well to be on the lookout for any *specially large* or *specially pale* corpuscle. Such a one will catch the eye if we

[1] In cold weather both slide and cover should be warmed before using.

are on the watch for it, even though the slide is being passed along very rapidly, and all such should be carefully examined.

Another thing to watch for is anything *black or dark brown.* If the slide is not perfectly clean, or if the cover-glass has touched the skin in collecting the blood, there will often be black spots which make us pull up short and examine, only to find that they are bits of dirt. This loses time, and hence, as above noted, the importance of care and cleanliness in the earlier stages of the process.

Besides any strikingly pale or swollen corpuscle or any black dots, we should be on the lookout for any *movements* in the field. Here again cleanliness saves time. In dirty slides I have repeatedly found rapidly moving organisms unknown to me but clearly not the malarial organism, and wasted time in making sure that they were of extraneous origin.

III. *The Malarial Organism.*—(*a*) "Hyaline Forms." In the earlier stages of its growth, *i.e.*, during and soon after the chill, the organism is not pigmented, but appears only as a light spot in the pale greenish-yellow of the corpuscle. It practically is never to be seen outside the corpuscle. All malarial organisms are to be found within the corpuscle, and *only there.*[1]

For those who have not examined many specimens of malarial blood it is a very difficult thing to find the organism at this stage of its growth, and the number of mistakes in diagnosis is very large.

In the later stages, when the organism has become well pigmented, there is nothing that at all resembles it, and those who have seen and watched it a few times can hardly mistake anything else for it. Not so with the so-called "hyaline" or youngest form of the organism. Personally I think the name "hyaline bodies" is responsible for a part of the mistakes. We are led to expect something more shiny and refractile than the organism really is, and so are misled by the brilliant white circles to be found at the centre of many normal corpuscles under certain conditions of light and partial drying up. Time and again I have been asked to look at malarial organisms (always the "hyaline" forms), and found nothing more than one of these effects of light which can be found in any normal blood, if the

[1] Except degenerate forms and spores at the moment of segmentation (*rarely* to be seen). Crescents and ovoid bodies are intercellular.

conditions are right. There are certain marks by which we can exclude these artifacts from consideration:

I. They are generally far too numerous to be malarial organisms. One usually finds a dozen or more in a field which would be almost unheard of with the plasmodium malariæ.

II. They are generally in the centre of the corpuscle, while the young malarial organism is almost never at the centre.

III. They are almost invariably round, the malarial organism being generally more irregular and branching.

IV. They seem to increase and diminish in size as we focus up and down upon them, while the malarial organism only grows dimmer or clearer.

V. They are, as before mentioned, more brilliantly white and shiny than the malarial organism, which has often a faint tinge of yellow, although much paler than the surrounding corpuscle substance.

VI. Their edges are sharper, the malarial organism often fading off very gradually into the corpuscle color.

VII. Their movement is different. The malarial organism is not at all the only thing to be seen moving in the blood, as has sometimes been stated. The red corpuscles have the Brownian motion, and as they begin to crenate often move very actively. But their motion is very different from that of the hyaline malarial organism, for the latter changes both its shape and its position in the corpuscle quite rapidly, while the motion of the light space in an ordinary red cell is a wavy undulation of the outlines back and forth without any considerable change of shape.

(*b*) As soon as the organism gets any pigment (and there are very few times in the cycle of a malarial case when there are not *some* pigmented organisms present), the active rapid motion of the black pigment dots is unlike anything else seen in the blood, and when once recognized can never be forgotten or mistaken. It is only when the pigment has ceased moving (owing to the death of the organism) that the differentiation between dirt and malarial pigment becomes difficult.

Sometimes it is really difficult to distinguish motionless pigment in a malarial organism from dirt even on careful scrutiny. The best way is to get a fresh slide when the pigment is in motion.

To any one fairly familiar with the appearance of pigmented forms of malarial organisms, failure to find them in a case of malaria is due generally (1) to too thickly spread a layer of blood, the corpuscles overlying each other; (2) to not looking long enough (Figs. 19 and 20).

I have not attempted to go into the marks by which we can

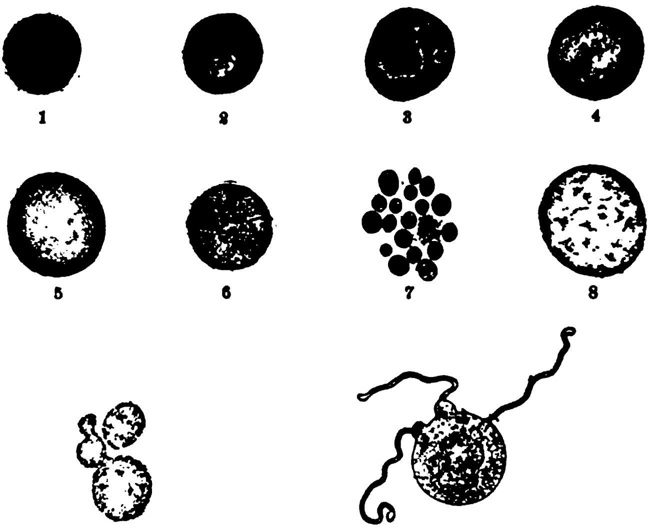


FIG. 19.—The Parasite of Tertian Fever. 1, Normal red cell; 2, hyaline form of malarial parasite; 3, 4, 5, pigmented forms of malarial parasite; 6, 7, segmenting forms of malarial parasite; 8, 9, degenerating forms of malarial parasite; 10, flagellate form of malarial parasite. (After Thayer.)

differentiate the tertian, quartan, and æstivo-autumnal forms of the organism—for clinical evidence usually suffices to determine this point. For information on this and all the finer points in regard to the life history and habits of the organism W. S.

FIG. 20.—The Parasite of Quartan Fever. 1, 2, Pigmented forms; 3, segmenting form; 4, flagellate form. (After Thayer.)

Thayer's admirable monograph should be consulted. Here it is sufficient to say that as the paroxysm draws near, the pig-

ment granules begin to work in towards the centre in radiating lines until they are all collected in a solid black mass. While this is going on, the pigment granules not infrequently gather into short rod-like masses not at all unlike bacilli.

Round the central mass of pigment, indistinct radiating divisions may sometimes be seen just before the organism breaks up. These divisions have been compared to the petals of a flower, but it is very difficult to see more than the faintest indications of such an arrangement in most specimens. The corpuscle itself is by this time wholly lost to sight.

(*c*) The next stage, that of segmentation, is less commonly seen than those just mentioned, and is only to be satisfactorily observed by using a warm stage (*vide supra*, page 8) and spending considerable time on the watch for it. Around the central pigment mass we may sometimes see in ordinary specimens (without warm stage) the faint outlines of a group of small spherical, colorless bodies (*vide* Fig. 2, 9, Plate I.) which are the new generation of young organisms.

Now we should expect that with the next step in the process we should find these young plasmodia free in the plasma or entering a fresh set of red corpuscles. But in the peripheral circulation this is rarely if ever observed. Thayer in his immense experience has never seen them. The next evidence we have of the organism is as a "hyaline" body inside the corpuscle again.

Almost all stages of the growth of the plasmodium which we can watch in the blood drawn from the peripheral circulation take place within the corpuscle. It is true that as the pigmented organism gets towards its full growth, and before the granules have begun to gather at the centre, we may find it very difficult to find any trace of corpuscle substance around the margin of the plasmodium. Sometimes we see a ring of non-pigmented glistening white substance outside the moving black dots (see Fig. 2, 7, Plate I.) standing out light against the darker plasma. Whether this be corpuscle substance or not I do not know. It is not described or pictured in the standard works on the subject.

Occasionally we do find pigmented bodies wholly outside the corpuscle, either partly or fully grown. In the intracorpuscular forms the distinction between plasmodium and corpuscle substance is not, I think, so sharp and clear as one would be led to expect from the plates in standard works. With average eyes

and lenses the outline of the organism, as distinguished both from its pigment granules and the surrounding corpuscles, is not easy to see. It is the moving pigment granules that attract our notice.

(*d*) It remains to speak of three comparatively small points:

1. The presence of flagella.
2. Pigmented leucocytes.
3. Crescents.

1. Toward the end of the life history of a malarial parasite, it sometimes makes its presence very obvious in the microscopic field by knocking about the surrounding corpuscles with its arms or "*flagella.*" Exactly why and under what conditions it shows or fails to show these appendages is not known. They are about two or three times as long as a red corpuscle and one-third or one-fourth as wide. They are usually to be inferred rather than directly seen, as they are nearly transparent. Our attention is attracted by an active motion among a group of red cells apparently of spontaneous origin. Gradually we make out a filmy whip-like tail attached to an adjacent malarial parasite. Sometimes there is pigment dotted along the flagellum itself, and then we can make it out much more easily. Its distal end is especially apt to be pigmented, and by the help of this pigment we make out that it is bulbous, while similar swellings can sometimes be seen at other points along the flagellum. Such a flagellum may break off and dart about free among the corpuscles. As the pigmented end is sometimes all that we can see of it, this gives rise to the appearance of a very small, *actively locomotive* pigmented body free among the corpuscles and its course may be followed through several fields.

When the flagella have ceased moving, their presence is generally detected, if at all, by an irregular line of pigment dots about 20 μ long, which will be shown by careful focussing to be contained within a nearly transparent membrane.

Very often we find a leucocyte in process of closing round the flagellated parasite.

2. Pigmented leucocytes, containing the whole or part of malarial organisms or simply blocks or granules of black pigment, are usually to be found in the blood near the time of the chill. The pigment is to be carefully distinguished from the granules present in most leucocytes, which in certain lights look

quite dark even if unstained, dark enough to be mistaken for pigment by the untrained eye. Careful focussing and changing the light will easily determine which we are dealing with, provided we are familiar with the appearances of leucocytes in the fresh unstained blood. In certain forms of the disease in which the organisms themselves retire to the internal organs, the presence of

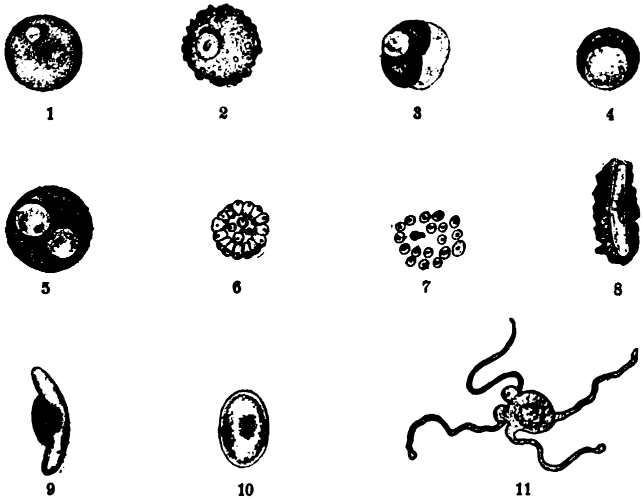


FIG. 21.—The Parasite of Æstivo-Autumnal Fever. 1, Hyaline form; 2, ring-like form in shrunken cell; 3 shows retraction of hæmoglobin about the parasite; 4, 5, development of parasite; 6, 7, segmenting parasites; 8, 9, crescents; 10, ovoid body; 11, flagellate form. (After Thayer.)

pigmented leucocytes may be the only evidence of the disease to be found in the peripheral blood and is therefore of the greatest importance.

3. Crescentic forms are not often seen in New England. They are found only in the æstivo-autumnal forms of malaria which occur chiefly in the South and West and have been seldom reported in any Northeastern State except in patients who have brought them from the South and West. I have never seen these crescentic forms except in the stained specimens of other observers, and my ideas of them are mostly second-hand (Fig. 21). Full account of them will be found in the monograph of Thayer's above referred to.

Hitherto I have spoken wholly of the appearance of the par-

asites in the fresh unstained blood, this being by far the simplest, easiest, and surest way of finding them and the only way of studying their development. In cases in which we cannot make a microscopic examination at the bedside, we can sometimes preserve the organism alive between slide and cover-glass, until we can get it to the nearest microscope, even if this takes several hours. I have carried specimens in my handbag a whole morning and yet found the pigment of the malarial parasite in motion at the end of that time. Warm weather favors this. When it is necessary to keep the specimen some time before examination, it is best to paint on the slide a ring of vaseline or any gummy substance, and allow the drop of blood to spread out inside this ring so that the margins of cover glass are glued to the slide by the oily substance and the entrance of air is prevented. The cedar oil ordinarily used for immersion lenses answers the purpose very well. Both slide and cover should be gently warmed before spreading the drop of blood.

Many physicians who cannot possibly carry a microscope about with them can easily find room for a few slides and cover-glasses and they may be of great service.

When specimens have to be sent by mail, or for long distances, or in cold weather we have to fall back on dried specimens prepared as described on page 32, provided always that a bedside examination is impossible. These can be stained by one of the following methods:

Leave the specimen for half an hour or more in equal parts of ether and absolute alcohol, dry them in the air, stain for from one-half to five minutes in a one-half-per-cent solution of eosin in sixty-per-cent alcohol, wash in water, dry and stain one-half to one minute in concentrated watery solution of methylene blue; wash again in water, dry in filter paper, and mount in Canada balsam.

Personally I have found this method rather unsatisfactory on account of the different intensity of different eosin stains and the consequent need of finding out by experiment how long (within the limits of one-half to five minutes) the specimen is to be stained before a distinct yet not violent red color is attained in the protoplasm of the corpuscles. The blue stains the plasmodium itself in contrast with the pink corpuscle substance around it; the pigment granules remain, as in

the fresh specimen, black or brownish black. (See Fig. 3, Plate I.)

In my hands the stain of Plehn has proved much simpler and more satisfactory as well as quicker. By this method we leave the specimens only three or four minutes in *absolute alcohol* and then stain five or six minutes in the following mixture:

Concentrated watery solution methylene blue............	60
One-half-per-cent solution of eosin in seventy-five-per-cent alcohol..	20
Distilled water..	40
Twenty per cent NaOH.....................................	12 gtt.

Wash in water and mount in Canada balsam.

The trouble of double staining and the uncertainty as to the length of time are avoided by this solution, and the parasites are beautifully stained. The ordinary Ehrlich-Biondi mixture may also be used to demonstrate pigmented forms. The organism itself does not stain at all with this mixture but stands out light against the yellow of the corpuscle, the pigment looking as it does in the live parasite. The hyaline forms need some other stain for satisfactory recognition, but it is sometimes convenient to use the same stain for the differential count and the malarial organism, as for instance when we have only one cover-glass preparation in a case of doubtful diagnosis. Fixing the specimen in alcohol and ether is here far better than heat; otherwise the technique is as above described under Triple Staining (page 33). The general appearance of the organism so stained is shown in Fig. 22.

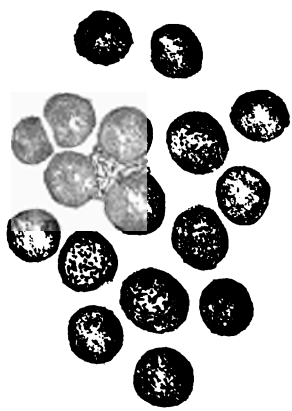


FIG. 22.

If the organisms are fairly numerous and the technique is good we can find them by this method even in preparations months old. In general, however, it is very inferior to the ex-

amination of the live organism in the fresh blood, and gives many more chances for error.

So much for technique.

We often hear reports of fruitless search for the parasite in the blood of malarial patients, but the regularity with which they are found at all the larger hospitals and by all practised observers in this and other countries leaves no doubt that they are to be found in every case during some portion of the cycle. The practice of taking blood during a chill contributes, I believe, to the number of unsuccessful endeavors to find the organism; as mentioned above, this is the worst, not the best time to look for them. Too thick a layer of blood between slide and cover accounts for some failures, as I have found in personal experience.

No doubt, in many cases in which we fail to find the organism in supposed malaria a faulty diagnosis is the reason. Many of the cases in which latent malaria is supposed to have "come out" after a surgical operation are exploded by the negative examination for parasites and the positive indications of pus-pocketing which are afforded by a marked leucocytosis (never present in simple malaria), and the fact of insufficient wound drainage is often disclosed in this way. Whenever we see the leucocytes increased we begin to doubt the existence of an uncomplicated malaria; if, furthermore, we see no signs of any pallor of the corpuscles we doubt the presence of malaria still more, as there is no more rapid deglobularizer than the malarial organism.

How long after a chill the organisms may still be found in the peripheral blood is difficult to decide, but certainly they can be found any time within twenty-four hours after the last chill, unless quinine has been given, and sometimes even if it has been given.

Other Changes in the Blood.

Red Corpuscles.—The following is from Thayer's remarkable monograph:

"A reduction in red corpuscles follows each paroxysm; these reductions are more marked after the early paroxysms than after those occurring later. When a certain degree of anæmia has

been reached the losses per paroxysm are much less. When the number of corpuscles is reduced to 2,000,000 or 1,000,000 there is little tendency toward a further fall; sometimes there may be slight rises in the curve between the paroxysms; often, however, the number of corpuscles remains stationary for weeks.

"In pernicious cases the number of corpuscles may fall between paroxysms." Kelsch has seen the count decrease to as small a number as 500,000 per cubic millimetre. The diminution is greater the longer the disease lasts and the more in tense its manifestations.

During the paroxysms, particularly the earlier ones, the red cells tend to *increase* in number.

In tertian and quartan fevers there is a rapid and almost complete restitution of the corpuscles during the afebrile period.

In æstivo-autumnal fevers the number of red cells bears a direct relation to the number of organisms. Crescentic bodies seem to have no influence on the number of red cells.

When after a paroxysm the number of corpuscles has been greatly diminished the succeeding paroxysm may be followed by a slight reduction only or even by an increase.

Bignami and Dionisi distinguish three types of post-malarial anæmia:

1. Ordinary secondary anæmia, but with leucopenia instead of leucocytosis; such cases usually recover.

2. Anæmia practically identical with pernicious anæmia, megaloblasts being present, and ending fatally.

3. Anæmias which are progressive, because the bone marrow cannot compensate for the losses of corpuscles.

The rapidity of the diminution in red cells may be very great. Kelsch's count of 500,000 cells per cubic millimetre, mentioned above, was after thirty days' illness. Grawitz has seen a loss of 4,000,000 cells in six days.

Qualitative changes are those of severe secondary anæmia, deformities in size and shape, normoblasts, occasional megaloblasts in the worst cases, motility in the "pale, ghostly" cells.

Hæmoglobin.—The loss of hæmoglobin bears usually a direct relation to the number of parasites in the blood. As a rule, the corpuscles and hæmoglobin are diminished proportionally (color

index =1) but sometimes the hæmoglobin is reduced disproportionately.

In convalescence the restitution of hæmoglobin is often incomplete; persons living in malarial districts have often a slightly smaller percentage of hæmoglobin than those living elsewhere.

The rapid diminution in hæmoglobin is a valuable point in differential diagnosis between malaria and typhoid or pneumonia.

White Cells.—The number of leucocytes is usually subnormal, but show a slight increase at the beginning of the paroxysm. Following this increase there is a rapid decrease continuing throughout the paroxysm. The small number of leucocytes is to be seen at the end of the paroxysm when the temperature is subnormal. From this time it shows a gradual increase until the beginning of the next attack (Billings).

In a general way the white cells follow the same course as do the red.

The differential count shows a lymphocytosis whenever the white cells are subnormal, the larger forms of young cells being especially numerous, while the adult cells and eosinophiles are scanty.

In four cases of post-malarial anæmia Billings found quite marked leucocytosis.

The occurrence of pigmented leucocytes has already been mentioned.

Grawitz and others have noticed an increase of eosinophiles in post-malarial anæmia.

FILARIA SANGUINIS HOMINIS.

Although most commonly found in tropical countries, one species of this worm is not very uncommonly found in various parts of the United States. Any case of chylous urine or elephantiasis should lead us to make a careful examination of the blood for the filaria. There are at least four species of filaria, one of which is present in the blood chiefly at night, another chiefly during the daytime, and another continuously. Only the *filaria nocturna* has thus far been seen in America (Fig. 23).

In examining for the filaria a slide of the fresh blood is pre-

pared in the usual way, *but after 8:30 o'clock in the evening,*[1] and examined at once. The embryo of this parasite (which is what

FIG. 23.—The Filaria Sanguinis Hominis. The head, curled up, is seen at the right of the cut, the tail at the left. Instantaneous photomicrograph. Four hundred diameters magnification.

we find in the human blood) is from one-ninetieth to one-seventieth of an inch in length, *i.e.*, about fifty times the diameter of

FIG. 24.—Tail of Filaria, showing prolongation of the sheath beyond the end of the embryo itself. Magnified 800 diameters.

a red cell, and about the width of a red corpuscle. Seen in the blood it retains its vitality and motile power for a considerable

[1] In persons who sleep in the daytime and work at night the habits of the filaria are said to become reversed, so that it appears in the peripheral circulation chiefly in the daytime, and is to be looked for then.

time, so that its motions may continue a week or more between slide and cover-glass. Cold has little effect upon it, even freezing temperature failing to do more than make the movements slower.

A distinction can generally be made out between the embryo proper and its sheath (see Fig. 24). From this sheath the embryo escapes when in the blood of the mosquito, which insect

FIG. 25.—The Movement of a Single Filaria during Four Successive Exposures of one-fifth of a second each, the entire series occupying less than five seconds. Magnified 300 diameters.

acts not infrequently as intermediary host and conveys the parasite indirectly from man to man through the medium of water. After sucking in the organism with the blood the mosquito lays its eggs and dies in some neighboring pond or stream whence the filaria again gains access to men.

It is a long, slender, snake-like, gracefully shaped worm, and when alive its activity is so great that measurements and observations of its structure cannot be made till it is paralyzed by approaching death (Fig. 25).

Posteriorly it tapers for one-fifth its length down to a very sharp point. The extreme end of the tail often looks as if ar-

ticulated, for it does not harmonize with the general curve of the body, but lies bent at an angle. Toward the head it tapers very slightly and when alive a "pouting" movement as if of breathing can be seen at its very extremity. About the middle of the body a granular aggregation can be made out along the central axis of the animal. Except for this granular portion the parasite is so translucent that it is not easy to make it out at first.

Fig. 26.—Head of Filaria. Shows structure and beginning granular degeneration. Magnified 1,500 diameters.

The distinction of body and sheath mentioned above, appears as a "clear space" at each end of the body (*vide* Fig. 24) After the motions have ceased it becomes darker and traces of transverse striation may be seen (Fig. 26).

It has no locomotive power and confines itself to wriggling in the same spot. Saussure[1] says he has watched them "fighting with each other for hours."

The head of the filaria is said by some authorities to be supplied with feelers or flagella, and Manson describes what he calls a "cephalic armature" or fang (Fig. 27).

[1] Philadelphia Medical News, June 28th, 1890, where he reports twenty cases seen in Charleston, S. C.

The same organism can sometimes be found in the chylous urine, but not every case of chyluria is due to the filaria sanguinis hominis. In a considerable proportion of cases no such organism is to be found.

Henry (*Med. News*, May 2d, 1896) succeeded in staining the parasites *intra vitam* by giving the patient considerable doses of methylene blue internally for some weeks. Only a faint

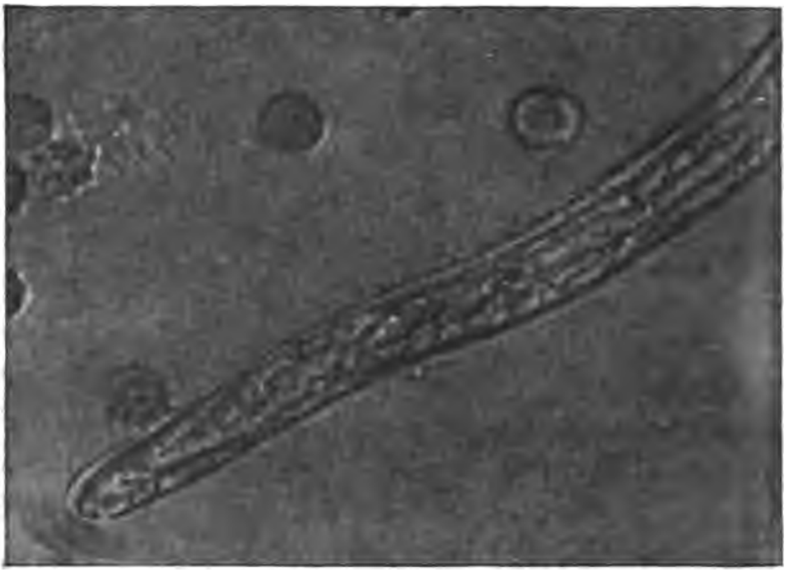


FIG. 27.—Head of Filaria Magnified 1,500 Diameters. The blur in front of the head may be due to the motion of flagella.

bluish tinge was imparted, however, to the organism by this method.

For finding the parasite it is best to use a low power, not an immersion lens, and the whole of several slides should be looked over.

Specimens can be dried and preserved for staining provided we do not heat them over a lamp or pass them through a flame. Manson[1] stains with eosin and mounts in "glycerin jelly" (Fig. 28).

Several other species have been observed in England in

[1] The "Filaria Sanguinis Hominis," by Patrick Manson, M.D., Amoy, China, 1883.

negroes from the Congo River, but not hitherto in America. But as it frequently is to be found in persons who have no symptoms whatever, it may well be that some of these other species would be found here if one took the trouble to seek out natives of Southern China (one out of every ten of whom carries

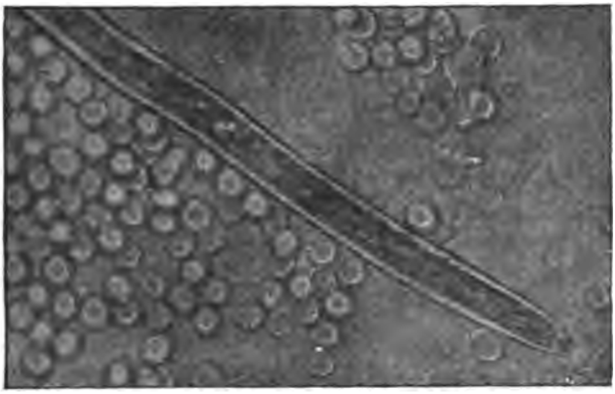


FIG. 28.—Head of Filaria Overlapping a Red Corpuscle. The appearance might be mistaken for the cephalic end of a sheath.

about the filaria in his blood), or of Central Africa, or other tropical regions.

SPIROCHÆTE OF RELAPSING FEVER.

During the febrile paroxysms of relapsing fever, and for one or two days before them, Obermeyer and others have found constantly present in the peripheral circulation a parasite whose length averages about six times the diameter of a red corpuscle. Even under high-power lenses it is a mere thread in width, curled upon itself like a corkscrew and actively motile, so that in examining the blood with a low power we get "a peculiar impression of disturbance" among the red cells.

The number of twists in this spiral-shaped organism varies a good deal, and one of its motions consists in contracting and extending itself like a spiral spring. It can thus multiply its own length three or four times. It has also a delicate, wavy, but rapid motion along its long axis. The whole thread, or a part of it only, may have these motions. Further, the whole parasite has power of locomotion apparently independent of the currents

in the blood plasma of a slide and cover-glass specimen. Its locomotion is slow compared to the movements above described. Particularly in the blood post mortem they are apt to wind themselves into each other so as to seem much larger than they actually are, and sometimes a large "nest" of them may look like a leucocyte, except for the fine, wavy threads which can be seen in motion at the periphery of the mass.

The number present in the blood is very much smaller at the beginning of a paroxysm than after the second day. During the first few hours of a febrile period Mocyntkowsky could find only one spirochæte in ten or twenty microscopic fields, while later on he saw twenty or thirty of them in a single field. There are usually more parasites with each successive paroxysm.

Blood taken from different parts of the body often shows a great difference in the number of organisms to be found. The life history of a single parasite seems to be very short, but they multiply with the greatest rapidity. Albrecht has seen them so increase within six hours that whereas at first he saw only a few in the whole slide he later found many in each field. As the spirochæte dies, its movements get languid and finally it breaks up into small granular bits (spores?).

Between paroxysms the spirochætes are not found, but there are to be seen peculiar highly refractile globules compared by v. Jaksch to a diplococcus. The latter author believes that he has seen these develop into the spirochæte at the beginning of a paroxysm and hence believes them to be spores.

This spirochæte is found in all cases of relapsing fever and in no other known disease, so that like the plasmodium malariæ it is pathognomonic and of the highest importance.

Anæmia and leucocytosis are among the secondary results of the presence of this parasite in the blood.

A certain resemblance has been noted between the spirochæte and a free flagellum broken off from a malarial parasite, but the clinical history and the presence or absence of other evidence of malaria in the blood would easily decide the question of diagnosis.

Technique of Examination.—As in looking for the malarial organism it is best to examine the blood fresh between a slide and cover-glass (*vide supra*, page 7) and to use an oil immersion lens. In dried specimens the organism can be stained

with fuchsin, but it is much more difficult to recognize than in the fresh blood.

DISTOMUM HÆMATOBIUM.

Bilharz found this parasite post mortem in the large internal veins (portal, splenic, mesenteric, etc.), but as it has never been seen in the peripheral circulation its clinical importance is thus far *nil.*

BACTERIA IN THE BLOOD.

(*a*) *Cover-Glass Specimens.*—Bacilli of anthrax, tuberculosis, glanders, grippe, typhoid fever, and tetanus have been demonstrated in the blood of human beings as well as have the pyogenic streptococci and staphylococci, the diplococcus lanceolatus, the gonococcus, and the bacillus coli communis. Nevertheless it is exceedingly difficult and frequently impossible to find them, and no considerable practical use has as yet been made of the cover-slip examination of blood for micro-organisms.

Gunther's method is an excellent one. Cover-glass specimens of the blood are prepared as above described (page 32), and left a few seconds in five-per-cent acetic acid to render the red cells invisible; the acetic acid is then shaken (*not washed*) off and the cover-glass held over the mouth of a bottle of strong ammonia water to neutralize the remaining acid. The covers are then stained with the Ehrlich-Weigert solution,[1] mounted in balsam, and examined with a one-twelfth immersion lens.

(*b*) *Cultures* (see above, page 35).

AMÆMIA DUE TO INTESTINAL PARASITES.

The bothriocephalus latus, ankylostoma duodenale, and a few other parasites are capable of producing by their presence in the intestine a very severe anæmia, which may be indistinguishable from pernicious anæmia. As yet no such case has been reported in this country, but Askanazy[2] and Schaumann[3]

[1] To 6 c.c. of distilled water add ten drops of aniline oil and filter. To the filtrate add a saturated alcoholic solution of gentian violet till slight (transient) turbidity appears. On the surface of this solution in a watch glass float the cover-glass face downward for twenty-four hours.

[2] Vereins-Beilage der Deut. med. Woch., 1895, Bd. 148.

[3] "Bothriocephalus-Anæmia," Berlin, 1894 (Hirschwald).

have carefully studied the disease in Germany and found that the blood may correspond exactly with that of pernicious anæmia, including the presence of high color index and of a majority of megaloblasts among the nucleated red cells present. Yet such cases may be rapidly and permanently cured by expelling the parasites from the intestine. No special description of the blood states need be given, as they present nothing peculiar.

CHAPTER XII.

THE BLOOD IN INFANCY.

I. *All the signs by which sickness is shown in the blood of adults are exaggerated in children.* Their blood is apparently more sensitive to the action of any morbid influence. Causes leading to but slight anæmia or leucocytosis in the adult, produce grave anæmia and very marked leucocytosis in children. Into the reasons for this I shall not attempt to enter. The increased toxicity of their serum compared to that of adults, and the relatively recent establishment of the functions for producing and destroying blood have been suggested as explanation.

Comparatively slight hemorrhages, gastro-intestinal or respiratory disorders, which would not impoverish an adult's blood may produce considerable anæmia in a young child.

II. All forms of anæmia in infancy are apt to be associated with enlarged spleen.

III. I have already alluded to the polycythæmia and leucocytosis of the new-born, and the gradual fading out of these relative abnormalities as the child grows up. In judgments as to the presence or absence of leucocytosis in infancy, these physiological variations are too often lost sight of, especially as the proper leucocyte count for any given infant depends not simply on its age but on the backwardness or forwardness of its development. As with the fontanelles, the growth of the blood toward adult conditions may be retarded by congenital weakness (infantile atrophy, marasmus) or inherited disease (tuberculosis, syphilis) as well as by acquired sickness (rickets, cholera infantum).

Under the influence of any of these drawbacks a sick child's blood may be no further developed at three years than that of a healthy child of eighteen months.

IV. When we remember that in early infancy the leucocytes differ from those of adults not only in number but in that the young leucocytes are relatively more numerous ("lymphocytosis of infancy"), we shall understand that any influence like rickets

or syphilis which retards development, will show lymphocytosis together with the increased leucocyte count. Qualitatively as well as quantitatively the blood reverts to a more infantile condition.

V. This shows itself not merely in the leucocytes but in the red corpuscles. During the first days after birth the infant's blood shows greater *variations in size and shape* than that of adults, as if the type were not yet quite fixed. The majority of authors also find a few normoblasts in the first few days of life. These are not invariably present, doubtless because in some children the blood at the time of birth is more developed than in others.

Under pathological conditions the red cells revert to this earlier type and deformed or nucleated corpuscles are plentiful. This is more marked than in anæmia of the same grade occurring in adults. An anæmia that shows but thirty nucleated erythrocytes per cubic millimetre in an adult might show ten times that number in a child.

VI. As we said before, all blood changes are exaggerated in infancy. This includes such physiological changes as the digestion leucocytosis or that following cold bathing as well as pathological leucocytosis and anæmia, and changes in the degree of dilution or concentration of the blood seem to be similarly exaggerated, as is seen, *e.g.*, in the physiological variations in the specific gravity of the serum (Hock and Schlesinger[1]).

VII. The *hæmoglobin*, though relatively high at birth and for the first few weeks, is lower than that of adults during the rest of childhood. The high percentages of the earliest weeks are not due to a polycythæmia, but to a genuine increase of hæmoglobin in the individual cells (Schiff[2]), color indexes being often over 1.

It is indispensable, therefore, that we should know the age and degree of development of a child before we can draw accurate inferences from its blood. In many of the cases reported in literature we are unable to judge whether the blood condition is pathological or not, because the age of the child is not given. For example, v. Limbeck[3] quotes a case of acute gastritis re-

[1] Hock and Schlesinger Centralb. f. klin. Med., 1891.

[2] Schiff: Zeit. f. Heilk., vol. xi., 1890.

[3] v. Limbeck: *loc. cit.*, p. 373.

ported by Fischl[1] as having an unusually high percentage of young leucocytes (59.4 per cent). But this is physiological in the first days of life and may have been so in this case, the age not being given.

Observations of this sort should always represent a comparison between the conditions present *before* and *during* the sickness in question.

Bearing these general considerations in mind, we shall be better able to find our way among the complications and perplexities of the blood conditions in infancy.

THE ANÆMIAS OF INFANCY.

As above mentioned, anæmic infants are apt to have enlarged spleens. This may be due either to the anæmia or to some disease accompanying or underlying the anæmia (*e.g.*, rickets, syphilis). It seems more probable that the hypertrophy is not directly or exclusively dependent on the anæmia, inasmuch as similar blood changes are found without splenic enlargement. By far the greater number of reported cases of severe infantile anæmia are accompanied or caused by such diseases as rickets and hereditary syphilis, both of which may cause splenic hyperplasia even when no anæmia is present. It seems probable that the anæmia and the enlargement of the spleen are alike symptomatic of an underlying disorder.

1. Some writers (*e.g.*, Luzet[2]) divide the anæmias of infancy into two classes: those with splenic enlargement and those without it. Luzet considers that the former class is severer than the latter and more apt to show large numbers of nucleated red corpuscles than those with normal-sized spleens. This classification, however, does not always hold. We may have very severe anæmia without splenic enlargement and splenic enlargement with slight anæmia, and the presence or absence of numerous nucleated red corpuscles is governed by conditions other than the size of the spleen.

2. Another classification of children's anæmias was proposed in 1892 by Monti and Berggrün ("Die chronische Anämie im Kindesalter," Leipzig, 1892). They divided the cases into

[1] Fischl: Zeit. f. Heilk., 1892. [2] Luzet: Diss., Paris, 1891.

the *mild* and the *grave*, each group being subdivided into those with leucocytosis and those without it.

Secondary anæmia of infancy =	Mild =	With leucocytosis.
		Without leucocytosis.
	Grave =	With leucocytosis.
		Without leucocytosis.

They rightly discard the term "splenic anæmia," corresponding as it does to no single set of blood changes. The above classification puts pernicious anæmia, leukæmia, and anæmia infantum pseudoleukæmica (v. Jaksch) in a different category.

(*a*) Mild cases of secondary anæmia show no deformities in the shape or size of the red cells. The color index may or may not be low. The cases with leucocytosis are much more numerous than those without it and more apt to have a low color index; in other words, the loss of corpuscle substance is greater and the cases are approaching the imaginary boundary between "mild" and "grave."

(*b*) The grave cases have poikilocytosis, and of course a greater reduction of corpuscle substance.

"Chlorotic" conditions, and most but not all those with enlarged spleen, come under this heading; also most of those due to hereditary syphilis, prolonged diarrhœa, and rickets.

In 1894 Monti[1] gave the following classified lists of the commonest antecedents of secondary anæmia in infancy:

1. Congenital, due to....	Syphilis, Tuberculosis, Malaria, etc.	In the mother during pregnancy.
2. Acquired..	1. Hemorrhage.	From navel. After circumcision. Scurvy, purpura, hæmophilia, Werlhof's disease, melæna.
	2. Other causes.	Inanition. Bad hygiene (lack of light, air, etc.). Post-febrile. Nephritis, diarrhœa, serous effusions. Syphilis. Rickets. Suppuration. Diseases of liver, spleen, bone, or lymph glands.

He points out that cases with leucocytosis are usually graver than those without it and may develop into pernicious anæmia;

[1] Wiener med. Woch., 1894.

also that the presence of leucocytosis does not point to malignant disease, suppuration, or any of the causes which usually account for it in adults.

Grave cases with leucocytosis in infants under twelve months are apt to develop into the anæmia infantum pseudoleukæmica, or into true leukæmia or pernicious anæmia.

On the whole, the division of Monti and Berggrün seems much better than that according to the particular causes, *e.g.*, "rachitic anæmia," "syphilitic anæmia," etc., for there is no particular set of blood changes that follows rickets, syphilis, or any other disease. In connection with various diseases of infancy, and particularly with those last named, we may have anæmia of any grade of severity from that reducing the red cells to 4,000,000 down to cases with only 500,000 red cells per cubic millimetre or even less. The worse the case is the more likely is it to be accompanied by leucocytosis and the more numerous will be the nucleated red corpuscles, always more numerous here than in anæmia of adults.

In *syphilis*, hereditary or acquired, the red cells may fall below 1,000,000 and the leucocytes may rise as high as 58,000 (Loos). The hæmoglobin may be proportionally diminished, or may be even lower than the percentage of red cells, so that a "chlorotic" condition obtains.

Such cases have been called *chlorosis*, but it seems better to confine this term to anæmia of unknown origin and favorable course occurring in women soon after puberty, since obviously secondary cases may have similar blood.

Rickets in a case observed by v. Jaksch caused a fall of the red cells to 750,000 and Luzet counted 1,590,000 in a similar case. The hæmoglobin is usually low, but Hock and Schlesinger found 60 per cent with 2,300,000 red cell, a color index of 1.2 +.

Leucocytosis may occur even when no anæmia is present. Hock and Schlesinger found 45,000 leucocytes in a rachitic child of sixteen months, sound in other respects and not anæmic. *Acute gastritis* causes at first only leucocytosis (with increased percentage of young forms). If it becomes chronic the reduction of red cells is severe. Hayem found only 685,000 red cells per cubic millimetre in an infant of two months, though recovery eventually took place.

In *tuberculosis* of lungs and peritoneum in a child of seven, Monti and Berggrün counted 3,230,000 red and 17,200 white cells with 52 per cent of hæmoglobin.

Qualitative Changes.

The exaggeration characteristic of all blood changes in infancy extends to the presence of nucleated red corpuscles, which in all forms of severe anæmia are very numerous. What has been described above (page 76) as the typical megaloblast, a large pale-stained nucleus in a very large cell (see Plate IV.), is relatively rare in infancy. The nuclei are almost always deeply stained whatever their size, and apt to be small. Dividing nuclei are very common, both by karyolysis and karyokinesis. These changes are most often found in the anæmias of the severest type and those which resemble leukæmia (see below, page 346), but may occur in any marked secondary anæmia. Polychromatophilic and "degenerative" changes are very common in severe cases.

The increased leucocyte count, so frequently found, is often made up of a majority of the young forms (lymphocytes). This change, as above said, is not characteristic of rickets, syphilis, or any other cause of anæmia, but is to be regarded as a mark of the arrest of development or reversion to an earlier type of tissues brought about by various diseases in early infancy. Sometimes the large lymphocytes and sometimes the small are in excess.

A further qualitative change already alluded to (see above, page 104) is the occurrence of *myelocytes*. We have seen that small percentages of these cells are not uncommonly seen in the anæmias of adults. Now this, like all other blood changes, is exaggerated in infancy. Myelocytes are more apt to appear and in greater numbers. Their presence is not characteristic of any one disease, but they are commonest in the severer types of secondary anæmia, such as those following syphilis and rickets. Their significance is about the same as that of normoblasts. At times, however, they are so numerous as to make us hesitate somewhat before we exclude splenic-myelogenous leukæmia.

This brings us naturally to the discussion of *the difficulty of distinguishing the different blood diseases in infancy*, which natur-

ally centres in the question of the existence and nature of the so called

"ANÆMIA INFANTUM PSEUDOLEUKÆMICA."

Von Jaksch's[1] decription of this disease (which he was the first to recognize) includes the following elements:

1. Grave anæmia—*e.g.*, 820,000 red cells per cubic millimetre in one case.

2. Extensive leucocytosis—*e.g.*, 54,660 white cells per cubic millmetre, in the same case.

3. Great variations in the form, size, and staining of the white cells.

4. Deformed, degenerated, and nucleated red cells.

Von Jaksch admits that none of these blood changes are characteristic of the disease, but thinks that its title to the position of a distinct and separate disease rests upon *clinical* data, the more important of which are: (1) A great enlargement of the spleen without any such accompanying enlargement of the *liver* as is usually found in leukæmia (the lymph glands are sometimes enlarged). (2) A relatively good prognosis. (3) Post mortem we find no positive evidence of leukæmia.

This description was given by v. Jaskch[1] in 1889. He stated the relation of white to red corpuscles as 1:12, 1:17, and 1:20 in the cases seen by him. Later he reported three cases in one of which the white cells numbered 114,150, and the red 1,380,-000. The differential counts are not carefully given.

Almost at the same time Hayem[2] reported a similar case, and noted the abundance of nucleated red corpuscles many of which were undergoing mitosis. This was verified by Luzet[3] in May, 1891 (*Arch. gén. de Méd.*), who reported two cases. His description of the disease differs considerably from that of v. Jaksch. He finds no greater difference between liver and spleen than often exists in true leukæmia. The course of the disease, though sometimes chronic, usually ends in death. The leucocytosis in Luzet's cases was less marked than in those of v. Jaksch and not greater than that occurring in many anæmias of children. He dwells particularly on the large number of nu-

[1] Von Jaksch: Wien. klin. Woch., 1889, Nos. 22, 23.

[2] Hayem. Gaz. des Hôpitaux, 1889, No. 30.

[3] Luzet: Diss., Paris, 1891.

cleated red cells, and the *frequency of mitosis* and considers *this* the most important diagnostic point.

Although Luzet's continues to use the name suggested by v. Jaksch, he describes the disease so differently that it is difficult to see why the same title should be given to it. He agrees with v. Jaksch in thinking that it is not simply a severe secondary anæmia due to syphilis, rickets, tuberculosis, or infectious disease.

Somewhat similar cases had already been described by various Italian writers (*e.g.*, Fede) under the title of "*Infective Splenic Anæmia of Infants.*"

Among others who have written on the subject are Baginsky,[1] Senator,[2] Fischl,[3] Andeoud,[4] Monti and Berggrün,[5] Felsenthal,[6] Raudnitz,[7] Epstein,[8] Alt and Weiss,[9] Hock and Schlesinger,[10] Crocq,[11] and Rotch.[12]

The majority of these writers report very little as to the differential counts of white corpuscles. An increased percentage of the adult forms is mentioned by many, but Rotch in a case with 1,311,250 red cells and 116,500 white cells found only 16 per cent of the adult variety with 46 per cent of small lymphocytes, 34 per cent of large lymphocytes, and 4 per cent eosinophiles. A second case had only 14 per cent of adult cells and 84 per cent of lymphocytes (large and small).

Von Jaksch noted the lack of any relative increase of eosinophiles, supposing this to be a means of distinguishing his cases from true leukæmia. Luzet, on the other hand, found eosinophiles numerous. (This of course has no weight for or against leukæmia.)

Klein (*loc. cit.*) noted the occurrence of myelocytes in small number.

[1] Baginsky: Arch. f. Kinderheilk., 1892, vol. 13.
[2] Senator: Berlin. klin. Woch., 1892.
[3] Fischl: *loc. cit.*
[4] Andeoud: Rev. de méd. de la Suisse rom., 1894, p. 507.
[5] Monti and Berggrün: *loc. cit.*
[6] Felsenthal: *loc. cit.*
[7] Raudnitz: Prag. med. Woch., 1894, p. 6.
[8] Epstein: Prag. med. Woch., 1894, p. 6.
[9] Alt and Weiss: Centralb. f. med. Wissenschaft, 1892.
[10] Hock and Schlesinger: *loc. cit.*
[11] Crocq: "Étude sur l'Adénie," etc., Brussels, 1891 (Lamartin).
[12] Rotch: Pædiatrics, 1895, p. 361.

The discrepancy of these different reports is suggestive.

The chief importance of the heterogeneous group of cases which have received the name of *anæmia infantum pseudoleukæmica* seems to me to be as a proof of the difficulty of distinguishing the various blood diseases in infancy.

Among the cases reported under this name are some which might be any one of the following list: Pernicious anæmia, secondary anæmia with leucocytosis, Hodgkin's disease, lymphatic leukæmia, and probably splenic-myelogenous leukæmia.

(*a*) Most of the few reported cases of pernicious anæmia in infancy have shown moderate leucocytosis (as compared with adult blood), a fact which deprives us of one of the means of distinguishing the disease from secondary anæmia. The reports as to nucleated corpuscles very rarely separate normoblasts from megaloblasts, and we have no way, therefore, of being sure on this important point. The high color index and large diameter of the red cells are occasionally seen in other anæmias of infancy and are not always present in pernicious cases. The great fatality of all kinds of anæmia in infancy prevents our calling a case *pernicious* because of a fatal termination. Enlargements of liver and spleen occur in many cases of each type of infantile anæmia, and occasionally in pernicious anæmia of adults. They do not, therefore, exclude pernicious anæmia in infancy.

Bearing these facts in mind, it is evident that some of Luzet's cases of "anæmia infantum pseudoleukæmica" may have been pernicious anæmia. Von Jaksch's own cases may have been either (*a*) Hodgkin's disease with leucocytosis, (*b*) grave secondary anæmia with leucocytosis (Monti and Berggrün), or (*c*) leukæmia.

(*a*) Hodgkin's disease, which v. Limbeck finds to be very common in infancy, may affect the liver and spleen and not the external lymph glands, and may be accompanied by anæmia and leucocytosis such as v. Jaksch describes. Epstein considers that this is the case, and denies the existence of any such disease as the anæmia infantum pseudoleukæmica.

(*b*) As any anæmia secondary to rickets or syphilis may have enlarged spleen and liver and marked leucocytosis, we cannot tell from v. Jaksch's description that we are not dealing in his cases with secondary anæmia.

(*c*) Since v. Jaksch does not give any accurate differential

count of the leucocytes, there may have been large numbers of myelocytes in his cases for all we know, or an overwhelming percentage of lymphocytes, *i.e.*, either type of leukæmia.

One of the cases reported by Rotch as "anæmia infantum pseudoleukæmica" had 80 per cent of lymphocytes in a leucocyte count of 116,500, the ratio of white to red cells being 1:11, and the nucleated corpuscles abundant. The external lymph glands as well as the liver and spleen were enlarged. How such a case is to be distinguished from lymphatic leukæmia without autopsy I cannot see. Large numbers of nucleated corpuscles with mitoses (present in this case) are to be found in any anæmia of infancy where the red cells, as in this case, have sunk as low as 1,311,500, and therefore do not exclude leukæmia.

Von Jaksch protests that his cases are not secondary to rickets or any other disease, but Fischl[1] in a careful study of all the published cases finds that out of a total of eighteen cases, sixteen had severe rickets and two hereditary syphilis.

The writings of Raudnitz, Ebstein, Felsenthal, Fischl, and v. Limbeck, which deny the separate existence of the anæmia infantum pseudoleukæmica, are convincing to me, and are reinforced by the few cases of bad anæmia in children which I have seen. We must distribute the cases of anæmia with leucocytosis and large spleen under pernicious anæmia, secondary anæmia, and leukæmia.

But our problem is not yet nearly solved. All we have gained is the belief that v. Jaksch's new disease does *not* help us to classify these doubtful cases. The difficulty is still very great. The following case illustrates this:

A male child of sixteen months with symptoms of grave anæmia, greatly enlarged spleen and slightly enlarged liver, showed the following figures: Red cells, 2,500,000; white cells, 22,000. Differential count of 500 cells showed: Young cells, 53.8 per cent (46.2 of the smaller type); adult cells, 29.4 per cent; eosinophiles, 6.2 per cent; myelocytes, 10 per cent.

While counting these, 147 nucleated red corpuscles were seen, of which 21 were normoblasts, 50 megaloblasts, and 47 microblasts; 6 showed mitosis in their nuclei.

The child died shortly after without any complication or intercurrent disease. No autopsy. No evidence of rickets or syphilis or other previous disease.

[1] Fischl: Zeit. f. Heilkunde, 1892.

Now I see no reason for supposing this to represent a new type of anæmia, and yet I cannot feel perfectly safe in classifying it as primary anæmia, secondary anæmia, or leukæmia.

(*a*) Primary or pernicious anæmia should have a lower count of red cells and a majority of megaloblasts. The percentage of myelocytes (ten per cent) is higher than in any other case of pernicious anæmia on record, though in one adult case with autopsy I found 9.2 per cent with a leucocytosis of 12,500, or 1,150 myelocytes per cubic millimetre, against 2,200 per cubic millimetre in this case.

(*b*) It is hard to call an anæmia secondary which kills with no complications and when there is no evidence of any disease to which it can be secondary.

(*c*) For splenic-myelogenous leukæmia the total leucocyte count and the percentage of myelocytes are very small. Still the leucocyte count may drop very low in leukæmia even without any inflammatory complication. Such a case is reported by Osler, in which the leucocytes fell to 7,500, of which only 300, or four per cent, were myelocytes.

Hayem (*loc. cit.*, page 864) in a ten months' child counted 2,712,500 red and 33,000 white cells, almost the same figures as in the case just quoted. [Hayem unfortunately gives no differential count, but apparently considers the case leukæmic because of the enormous number of nucleated red cells, many with mitoses.]

Morse's case of leukæmia in infancy had 2,900,000 red and 48,000 white cells. Twenty-one and four-tenths per cent of the leucocytes, or about 10,000, were myelocytes. The same abundance of nucleated red cells (some with mitoses) were here present as in Hayem's case, so that there is evidently nothing peculiar in their presence in the disease described by v. Jaksch, as Luzet supposed.

These cases show that leukæmia may at certain periods present just such a blood picture as was present in the above-quoted case and that the number of leucocytes in the leukæmia of infants may be no greater than that in any anæmia with the leucocytosis so common in children.

It seems to me the most natural conclusion to be deduced from these facts is that we meet with cases in infancy *which are apparently intermediate between leukæmia and pernicious anæmia.*

I have pointed out elsewhere that there are many points of resemblance between the two diseases. The case of leukæmia reported by Osler showed at one period—the period of remission—a fall in the number of leucocytes and in the percentage of myelocytes till the blood was practically that of pernicious anæmia.

Dr. Rotch's case (above quoted) is another in which the diagnosis seems to lie somewhere intermediate between the two diseases, anæmia and leukæmia.

The case which I have quoted above seems to me on the whole nearer to the type of pernicious anæmia than of leukæmia, and Dr. Rotch's nearer to the latter than to the former; but each is really intermediate, *so far as the blood goes*, between the two diseases. I have no intention of suggesting that the organic lesions in these cases are intermediate between leukæmia and pernicious anæmia. It is simply the blood that is so.

Engel's case, reported in Virchow's *Archiv*, Vol. 135, suggests the same thing. He calls the case one of "*pseudo-pernicious anæmia.*" Meylocytes were abundant.

Polymorphous Condition.

This illustrates that "polymorphous" condition of the blood which v. Jaksch supposed to be characteristic of the anæmia infantum pseudoleukæmica. The same thing was very marked in all the bad cases of anæmia which I have seen, including the case above mentioned, and a case of true leukæmia in a girl of eight. The impression one gets from the field of a stained specimen is that *no two white corpuscles are alike.* Every species is subdivided into several sub-varieties and all stages of degeneration are to be seen in each variety. But this is characteristic of any very severe infantile anæmia and not of any single type.

LEUKÆMIA.

In Morse's careful article of August, 1894 (*Boston Med. and Surg. Journal*), twenty cases of leukæmia in infancy are collected. As he rightly says, probably most of these cases were not genuine. Only one of them includes a differential count, and this is in a lymphatic case. Morse's is the only one of the splenic-

myelogenous type on record in which the diagnosis is made reasonably certain by a color analysis. Fischl in 1892 said that there was *no* case on record with a differential count. It seems to be actually the case, therefore, that we have only two genuine cases of leukæmia in infancy from which to generalize, both occurring in the practice of Boston physicians.

The first case, seen in 1890 by Dr. F. C. Shattuck, was apparently acute, the symptoms appearing only six weeks before death. Cover-glass preparations examined by W. S. Thayer showed a ratio of about 1 white to 20 red cells. The differential count[1] showed: Small lymphcocytes, 97.9 per cent; large lymphocytes, .7 per cent; "polynuclear" cells, 1.4 per cent; eosinophiles, .08 per cent.

The other case reported by Morse has been mentioned above. No generalization is possible until other cases shall be added to these.

[1] Reported by Thayer in the Boston Medical and Surgical Journal, 1893, vol. 128, p. 183.

PART VII.

EXAMINATION OF THE SERUM.

CHAPTER XIII.

THE CLUMP REACTION.

General Description.

Although this phenomenon is to be obtained in various infections, natural as well as experimental, and with various body fluids, I shall describe as a typical case of it the reaction which takes place when the blood serum of a patient ill with typhoid fever is added in certain proportions (*vide infra*) to a young bullion culture of well-certified and virulent typhoid bacilli. In a drop of such a mixture, examined between slide and cover-glass[1] with a magnification of 300 diameters or more (an immersion lens is not necessary), we notice, as soon as the serum and culture are mixed, *either* a marked slowing of the progressive movements of the bacilli *or* an unequal distribution of them in the different parts of the preparation, some parts showing the bacilli closely crowded, while in others they are more scattered. Whichever of these changes occurs first, the slowing of locomotion or the tendency to grouping, the other soon follows, and then both processes go on together, as admirably described by Biggs and Park:[2]

"Some of the bacilli soon cease all progressive movement, and it will be seen that they are gathering together in small groups of two or more, the individual bacilli being still somewhat separated from each other. Gradually they close up the spaces between them, and clumps are formed. According to the

[1] Hanging-drop preparations are often recommended, but a simple slide and cover-glass are as good for the purposes of this reaction.

[2] American Journal of the Medical Sciences, March, 1897.

completeness of the reaction, either all the bacilli may finally become clumped and immobilized or only a small portion of them, the rest remaining freely motile, and even those clumped may appear to be struggling for freedom. With blood containing a large amount of the agglutinating substances all gradations

FIG. 29.—Pure Culture.

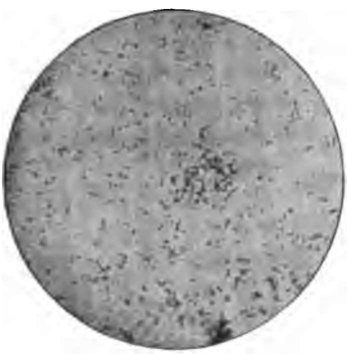


FIG. 30.—Partial Reaction.

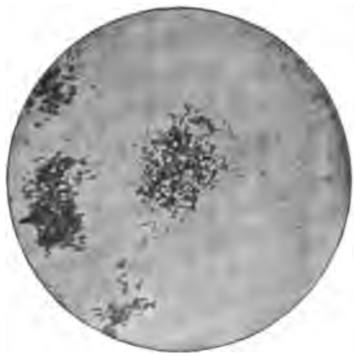


FIG. 31.—Typical Clumping.

in the intensity of the reaction may be observed, from those shown in a marked and immediate reaction to those appearing in a late and indefinite one, by simply varying the proportion of blood added to the culture fluid" (see Figs. 29, 30, and 31).

The process may go on gradually and be much more distinct at the end of half an hour.

The groups or clumps above described constitute the important part of the reaction for diagnostic purposes. Of the loss of motility more will be said later.

The clumps may hang together for a long time. They have been observed unchanged for one hundred and forty-four hours. On the other hand, they may be dissolved in a few hours and the bacilli regain their motility.

In watching the formation of the clumps it is easy to see that the bacilli are positively attracted to each other and do not drift passively into a heap. The loss of motility is not the cause of the clumping, as they often begin to approach each other while in vigorous motion. The power of locomotion is lost much sooner than are the squirming and spinning motions, which often persist among the bacilli in the peripheral parts of the clumps as well as outside them.

The clumps tend to adhere to the under side of the cover-glass.

Specimens can be fixed and stained with the bacilli in clumps —contrasting strongly with the even distribution of the bacilli in ordinary stained preparations.

Technique of the Clump Reaction in Typhoid Fever.

Our account of the methods of obtaining the clump reaction may be divided into the following parts:

1. The body fluids to be used and the methods of obtaining them.
2. The cultures.
3. Dilution and the time limit.

1. The Body Fluids to be Used.

Experiments have proved that the reaction can be obtained with the following fluids:

(*a*) The whole blood, fluid or dried.

(*b*) The plasma and serum, fluid or dried.

(*c*) The fluid obtained by blistering.

(*d*) The fluid *normally* present in the pericardium, pleura, peritoneum, and joints; *not* in rapidly accumulated effusions.

(*e*) The *milk* and colostrum of women suffering from typhoid during lactation.

(*f*) *Pus* from persons suffering with typhoid—whether the bacilli of Eberth are present in the pus or not.

(*g*) *Tears*—naturally (*i.e.*, gradually) secreted. If secreted in response to the irritation of ammonia fumes, the tears do not produce clumping.

(*h*) Some observers also find it in the fluid of œdema and in the bile. Others do not.

(*i*) The clumping persists in the above-named fluids after death and even in putrefaction. The "juice" of the spleen, kidneys, and rarely of the liver, will give the reaction feebly.

(*j*) Though present in the placental blood of pregnant typhoid patients, it does not usually exist in the fœtus.

The saliva, gastric juice, and sweat do not produce the reaction, so far as known. The aqueous humor sometimes does.

The urine and fæces sometimes do and sometimes do not give it, but these excretions in normal persons may also produce the reaction, so that they cannot be made clinically available.

Of all these fluids, the blood, the serum, and the fluid of blisters are the only ones used in clinical work, both because of their greater convenience, and because the clumping power is much more marked in the blood and blister fluid than in any of the others.

1. *Use of the Whole Blood—Fluid.*

The advantages of this method are (*a*) its quickness, and (*b*) the small amount of blood (*one drop*) sufficient for the test.

Its *disadvantages* are (*a*) that the corpuscles interfere slightly with the fields in which the reaction is to be watched, and (*b*) that they sometimes lead to the formation of false clumps ("pseudo-amas"), which simulate those present in the real clump reaction, and lead to false inferences. Both these objections are trifling, however, as the corpuscles can be excluded by waiting a minute or two until they settle, leaving a clear liquid above in which the reaction can be observed. The false clumps are rarely seen, and can be differentiated from the true by careful technique (see below).

I have used this method in many cases and always found it satisfactory and convenient. Widal, McWeeney, Delépine, and Coleman have employed it with success. It is most suitable for the "quick method" (see page 355), and is chiefly employed in this way.

Procedure.—Suck up some water with a medicine-dropper and

expel ten drops of it into a watch-glass. Then empty and dry the dropper, draw up from the watch-glass the ten drops just expelled, and mark with a file on the side of the dropper the point up to which the ten-drop column extends. Mark also the point to which one drop (expelled and then sucked up again as before) will rise.

Ten drops of the bouillon culture of the bacilli to be used are then expelled into each of several small test-tubes, and one of these tubes is carried to the bedside. After pricking the ear as if for blood examination[1] (see page 5), put the end of the medicine-dropper into the blood drop, and carefully draw back the rubber bulb (which has been previously pushed down over the glass part of the dropper) until the blood rises to the mark for one drop. Wipe from the outside of the dropper any blood that may adhere there and then expel the drop into one of the little test-tubes containing the ten drops of bouillon culture. In this way blood can be taken for examination from a dozen patients in as many minutes.

2. *Whole Blood—Dried.*

This method, though previously described and tested by Widal, was first put into effect in large numbers of cases by Wyatt Johnson, of Montreal, for the use of the Board of Health of Quebec, by whom specimens of dried blood sent by mail were examined and diagnoses returned as with diphtheria cultures. It was subsequently employed on a large scale by the Boards of Health of New York and Chicago.

The advantages of the method are (*a*) the ease and quickness with which the blood can be obtained, (*b*) the convenience for transportation by mail, and (*c*) that it does not deteriorate or become contaminated by bacterial growth, as specimens of fluid blood or serum are so apt to do. Its clumping power is fully equal to that of the serum *in most cases.*[2]

These advantages are very great and would surely lead to the

[1] Squeezing and milking the ear are of no harm in this procedure and enable us to get on with a trifling and painless puncture.

[2] Widal and Delépine think the fluid serum is slightly more powerful than the dried blood. Johnson admits that in one-tenth of the cases the serum is the more powerful. I have obtained reactions with the dried blood in only seven-eighths of the cases in which I got them with the fluid serum.

immediate and universal adoption of this method were it not for the following serious drawbacks:

(*a*) It is *difficult to measure the amount of blood* to be used in the test. This is important, because, as we shall see later, a positive reaction means not simply a clumping, but *a clumping in a 1 : 10 dilution of the blood*, to get which we need to know just how much blood we are dealing with. When we take the blood from a patient ourselves we can use the marked medicine dropper, as above described, but when blood is received through the mails for examination or taken by any one who does not measure it in some way, we cannot accurately gauge the dilution.

(*b*) It is agreed by all who have used the method extensively that the clumping may occur with the blood of healthy people and hence confuse our inferences. Whether these "false clumps" are due, as Widal supposes, to masses of fibrin and débris in which the bacilli become entangled, or whether they are formed in the ordinary way, there can be no doubt that they occur occasionally when dried blood is used.

These objections have led most observers to prefer the fluid serum, but when we have not the apparatus necessary for collecting and preserving fluid serum, or when such apparatus could not be transported, the method is of great value.

Procedure.—The blood should be dried either upon a glass slide or on a piece of glazed paper or card. Any absorbent substance is less available. Glass is easier to sterilize than paper. Several large drops should be placed in different parts of the glass or paper and *thoroughly* dried.

If paper has been used, we cut out the dried blood drop with a pair of scissors, keeping close to the blood all round, and drop it into a test-tube containing one or two drops of water, in which with some sharp-pointed instrument we mix the dried blood, freeing it as well as possible from the paper.

To the liquid so obtained add eight or nine drops of the bouillon culture of bacilli and proceed in the ordinary way. Or we may drop the fragment of paper holding the blood directly into ten drops of bouillon culture—using the bouillon itself to soak off the blood from the paper.

When the blood is collected on glass, it may be dissolved by putting water on the glass and rubbing the dried blood in it

until a decided red tinge is obtained. A drop of this mixture is then diluted and mixed with the bouillon culture. If I rightly understand the communications of Johnson on this subject, he does not pay much attention to the dilution of the mixture of dried blood and water, before examination. This cannot be too strongly insisted on. It is true that it is impossible to make *accurate* dilutions in most specimens of dried blood received for examination, but we must at least make the attempt and try to err on the side of diluting too much rather than too little.

A. The Fluid Serum—Quick Method.

The ear is pricked in the ordinary way and about twenty drops are forced out by strong squeezing. The blood is received in a small (preferably two-inch) test-tube, with the edge of which each drop is scraped off the ear; or we may suck the blood into a capillary pipette and expel it again into a test-tube or other receptacle. There is no need of cleansing the skin or sterilizing the test tubes in this method of procedure, as the whole process is finished up so rapidly that there is no time for contaminating organisms to grow.

The blood when collected may be at once centrifugalized, and the plasma used for the test, or we may wait till clotting occurs and use the serum. When blood is collected in test-tubes, it is convenient to free the edges of the clot from the tube all round with some sharp instrument, so that the serum may not be pinned down underneath the clot, as it often is. If this is done, a drop of serum can be had within two or three minutes, and is then mixed with ten drops of bouillon culture, as above described, and examined at once between slide and cover-glass.

(Dried serum can be used in the same way as dried blood, but has no special advantages and has not been frequently employed by any observer.)

B. The Fluid Serum—Slow Method.

This was the way originally described by Widal, or rather applied by him to the diagnosis of disease.

The serum must be collected *aseptically*, and many have therefore preferred to take it from a vein of the elbow, which is punctured with a sterile syringe, as described on page 35.

Durham cleans the skin of the ear with a two-per-cent solution of lysol, sucks blood into a sterile pipette, and blows it out again into a sterile test-tube to wait for clotting.

Or, if we desire to keep and transport the fluid serum, it is sucked into the bulb of a modified Pasteur's pipette (sterile), such as is shown in Fig. 32, which is then sealed by heat at the points A and B. In this way the serum will keep for an indefinite period and can be sent across the ocean, as was recently done at the request of the New York Health Department.

When we are ready to use the serum, one of the pointed ends of the sealed bulb is broken off and the serum expelled by gently warming the other end.

The serum aseptically collected by one of the above-described methods is then added:

1. To ten times its volume of bouillon culture of bacilli, *i.e.*, eight drops to five cubic centimetres of culture, in a test-tube, which is then left from eight to twelve hours in the thermostat at 37° C.; or

2. The serum may be added to ten times its volume of pure *sterile* bouillon, and then a trace of the dry agar culture of bacilli added with a platinum loop and *thoroughly* mixed with the bouillon by rubbing the loop against the inside of the test-tube, which is then kept twenty-four hours at 37° C. If the first of these ways is used, we get the effect of the serum on the fully grown bacilli; in the second way—which usually needs fully twenty-four hours—it works on the nascent and immature organisms.

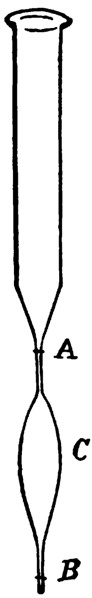


Fig. 32.

Whichever method is used, we find that within from eight to twenty-four hours a remarkable change takes place in the appearance of the culture when serum from a case, *e.g.*, of typhoid fever, is added to typhoid bacilli, nascent or full-grown. The uniform turbidity of the bouillon is gone and the liquid is either clear with an abundant flocculent sediment at the bottom of the tube, or is filled with coarse whitish particles separated from each other by clear bouillon. The latter change may take place the instant the serum is added to the culture, but usually needs from six to eight hours, and the full end reaction is often not completed till twenty-four hours elapse. Fraenkel

finds the reaction most marked in twelve to fourteen hours—less so in twenty-four (see Fig. 33).

A control tube containing the same proportions of the same culture and of a healthy person's serum should always be put into the thermostat along with the serum to be tested. Occasionally in such a control tube fine but visible whitish dust forms, *but such dust usually disappears later of itself, or can be dissolved* and the original diffuse turbidity produced *by shaking the tube,* while shaking a tube in which the true clump reaction has taken place will not break up the clumps nor restore the original turbidity.

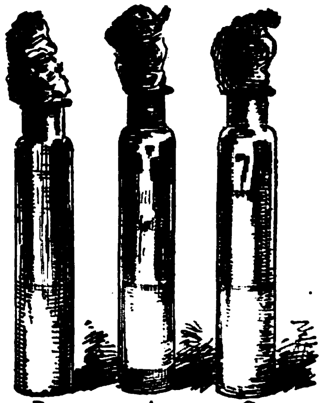


FIG. 33.—*A*, Complete reaction; *B*, *C*, controls.

As above suggested, the microscopical examination of the "dust" seen in such a test, or of the precipitate formed at the bottom of the tube, shows it to be made up of clumps of bacilli similar to those seen in the quick method, but generally larger.

The reaction is considerably less typical when the serum used is dark-colored, but the effects of shaking the tube and the comparison with the control usually enable us to decide.

Some precipitate and clumping may occur in cases not typhoid: (*a*) when the bouillon has not been filtered and contains sediment, in which the bacilli may become entangled; (*b*) when a large amount of the dry culture is added (in trying the slow method on nascent bacilli) and not thoroughly mixed with the bouillon; (*c*) in case the platinum loop is not quite cooled before the agar culture is taken upon it; (*d*) in case the culture is impure or the serum not aseptic.

3. *Blister Fluid.*

Biggs and Park find the fluid obtained by blistering the most satisfactory. A fly-blister the size of a five-cent piece is applied, and in from six to eighteen hours a blister has formed. The serum from the blister is collected with a capillary tube, the ends of which are then sealed. This serum is admirably clear and free from blood corpuscles and answers the purpose well.

This method has never been extensively used by other observers, except Puglieri.

Advantages and Disadvantages of the "Quick Method" and of the "Slow Method."—In favor of the quick method are: (1) *its quickness*, (2) the small amount of blood needed, and (3) absence of any need for asepsis and of any danger of contamination.

Against it are: (*a*) the occasional occurrence of pseudo-reactions or false clumps, which will be discussed on page 370; (*b*) that it needs a microscopic examination instead of being evident to the naked eye, as in the slow method;[1] (*c*) that it needs watching and cannot be left to "go on of itself."

In favor of the slow method are:

(1) That to some observers it appears more reliable and less apt to give pseudo-reactions.

(2) That it can be seen with the naked eye.

(3) That we do not need to watch it but simply to note the results at the end of from eight to twenty-four hours.

Against it are its slowness, the danger of contamination, the need of a large quantity of blood and of a thermostat.[2]

On the whole the great majority of observers prefer the quick method, and it has been used in three-fourths of the reported experiments. My own experience has been exclusively with the quick method.

Breuer, Catrin, and Vanlair and Beco are the only ones who distinctly prefer the twenty-four-hour method in all cases.

2. The Cultures of Typhoid Bacilli to be Used.

1. The stock cultures grow best on agar.

2. Ordinary neutral peptone bouillon, free from sediment, is the best medium for the test culture.

3. All observers agree that the cultures should be *young*—that is, that the transplantation to bouillon should have taken place not more than from twelve to twenty-four hours before the culture is used. Many observers find even the twenty-four-hour culture too old and prefer a twelve- to twenty-hours-old culture in all cases.

[1] Greene states that with the quick method a mottling of the specimen can be seen with the naked eye.

[2] Pick states that no thermostat is needed, and that sedimentation takes place readily at room temperature.

4. The virulence and motility of the culture are very important. All observers agree that the more virulent the culture the more readily and characteristically it is clumped by typhoid serum. Biggs and Park noticed that one culture of peculiarly great virulence recently received from Pfeiffer of Berlin worked much better in their cases than any other of the cultures used. I have repeatedly noticed that cultures recently taken from autopsies on patients who had died during the acme of the fever were much more easily clumped than those taken in autopsies on patients who had succumbed late, after the temperature had been normal for some time. I have also noticed that virulent cultures grown for a long time in the thermostat with weekly transplantations gradually lost a good deal of their susceptibility to the clumping power of typhoid sera.

Presumably these changes mean a loss of virulence in the culture, especially as they have always been accompanied by a diminution in the rapidity of motion in the bacilli. Cultures fresh from an autopsy usually show *furious* motility, the bacilli darting about like a swarm of insects, but after repeated transplantations and long sojourn in the thermostat a good deal of this motility is gradually lost. *Cultures kept at room temperature preserve their motility for much longer periods.*

For those who have no opportunity to test the virulence of organisms on animals, the motility is the best guide to virulence, and the rule should be: *Among the available cultures select that having the most rapid motility.*

4. Certain cultures contain small clumps of bacilli *before any serum has been added to them.* This is a very important point and has doubtless misled many. In consequence of this possibility every culture must be examined *each time* that a test is made. It is not sufficient to examine each culture once for all, as cultures vary slightly from day to day and also vary in different portions of the culture tube. For instance, ten drops taken from the middle of the bouillon may be found free from clumps, while if the next ten drops be taken from the surface or from the bottom of the liquid, they may contain clumps.

This point has been strongly insisted on by Widal, Rénon, and others.

5. It is hardly necessary to say that the cultures used must have been submitted to all the regular tests for the recognition

of the typhoid bacillus, and that the greatest care must be used to avoid their contamination.

The Use of Suspensions or Emulsions of the Bacilli instead of Cultures.

A few observers—particularly Durham and Grüber—have preferred to use a mixture of small bits of solid agar culture and bouillon instead of bouillon cultures. The majority of writers prefer cultures.

The Use of Attenuated Cultures.

Johnson found that with his methods of technique (dried blood and no definite dilution) pseudo-reactions were not uncommon with the blood of healthy people.

He proposed to avoid this by using attenuated cultures—*i.e.*, old stock agar cultures kept at room temperature and not transplanted more than once a month, from which he planted his bouillon cultures. This gives a bacillus of reduced virulence and slow, gliding motion, which is clumped far less readily than the virulent varieties. Bouillon cultures of this kind from twelve to twenty-four hours old he found to react in fifteen minutes with all typhoid sera and not with other sera even after forty-eight hours' waiting.

Durham, Biggs and Park, and Delépine, on the contrary, found such cultures unsatisfactory, in that it was not possible to avoid pseudo-reactions with sera of diseases not typhoid. I have been equally unsuccessful with this method, and believe with Biggs and Park that the most virulent cultures are the most reliable, if a proper technique is used. When dried blood *must* be used, the attenuation of cultures as advised by Johnson is probably a good plan.

The Clump Reaction with Dead Bacilli.

One of the most remarkable and interesting features of the clump reaction is the possibility of obtaining it with bacilli that have been killed by heat or by formol.

Widal observed that bouillon cultures of typhoid bacilli exposed to a temperature of 57°–60° C. for one-half to three-quarters of an hour lost scarcely any of their susceptibility to the clumping action of typhoid serum, though they are quite

dead. Higher temperatures (70°–120° C.) take away more and more of the susceptibility to clumping and *also cause the formation of false clumps without the addition of any serum whatever.*

Similarly one drop of ordinary formol mixed with one hundred and fifty drops of bouillon culture of Eberth's bacilli kills them, but apparently "embalms" them, so that their susceptibility to clumping is scarcely if at all lessened, even after the lapse of five months.

The bacilli gradually sink to the bottom of the tube, but when shaken up distribute themselves evenly throughout the medium and can be used like fresh cultures for diagnostic purposes. Bordet has noted the same thing with cultures of the cholera-vibrio killed with chloroform.

These facts seem at first sight to conflict with the statement made above, that fresh, motile, and virulent cultures are best, and that old ones are not reliable. But it may be, as Widal supposes, that the rapid action of heat or formol on virulent cultures preserves unchanged the power which prolonged growth in old media destroys. If this be true, it will enable us to dispense with our thermostat and careful nursing of cultures, since a single first-rate culture can be thus "embalmed" and preserved for use at all times and under all circumstances.

Widal's results with this method have not yet been confirmed by others.

3. Dilution and the Time Limit.

I. Dilution.

We have mentioned without explanation in various parts of this chapter that the blood serum or other fluids used must be diluted with at least ten times their volume of bouillon culture before any observation is made as to their action on the bacilli of typhoid fever.

The reasons for this dilution and for the proportions 1:10 are the following:

It has been found, as mentioned above, that the mere formation of clumps in bouillon cultures of Eberth's bacilli is not a power exclusively possessed by typhoid serum. The serum of

persons suffering from other diseases and even of healthy persons will form clumps exactly like those formed by typhoid bacilli, *provided it is not diluted.* The only known peculiarity of the typhoid serum is that its clumping power is *greater* than that of other diseases, and persists in spite of dilution, while the sera of diseases other than typhoid lose their power to clump typhoid bacilli when diluted ten times or more.

II. Time Limit.

But even this statement must be further limited. The sera of various other diseases, and of healthy persons, will sometimes clump typhoid bacilli *even in a 1:10 dilution, provided we give them time enough.* We must therefore limit the period within which a serum must "come up to the scratch" and do its work, if it is to be considered a typhoid serum.

Following Grüber and Durham, a time limit of *one-half hour* has been adopted by Grünbaum, Block, Haedke, Park, and others.

All that these more or less arbitrary figures stand for is this: that *hitherto no one has reported any considerable number of cases in which the serum of any disease or of healthy persons has clumped typhoid bacilli within one-half hour, when diluted 1:10 and used with unimpeachable technique.*

Johnson seems to be careless as to the amount of dilution, and Widal has not thus far admitted the necessity of a time limit, but the majority of careful and non-partisan observers are agreed that these precautions are necessary. If at any time cases are reported in which, despite these precautions, a clumping of typhoid bacilli has occurred with non-typhoidal sera, it will be necessary to raise the dilution to 1:15 or 1:20. Indeed there are some who think it should now be placed at one of these two figures.

The clump reaction in typhoid fever is to be considered specific and pathognomonic only in the sense that it occurs more readily and in presence of greater dilution in typhoid than in any condition yet reported. (For details and exceptions on these points see page 370.)

The serum of most cases of typhoid fever during the second week will clump typhoid bacilli even when diluted 1:40, and many sera preserve the power even at 1:100 or higher. The

following table from Biggs and Park illustrates these points well:

Case.	History, symptoms, and diagnosis at time of taking blood specimens.	Corrected diagnosis on completion of illness.	Reaction of bacilli in broth cultures to serum in different dilutions.		Reaction.
			Amount of serum.	Amount broth culture.	
1	Adult; sick four weeks, continuous high fever; pleurisy; "tuberculosis" with possibility of typhoid.	Tuberculosis.	1	1	Not appreciable.
2	Boy; sick two weeks; continued moderate fever, abating when test was made; prostration, constipation; no typhoid symptoms except fever and prostration; "atypical typhoid fever."	Uncertain.	1	1	Not appreciable.
3	Adult; symptoms of acute articular rheumatism only; "acute articular rheumatism."	Acute rheumatism.	1 1 1	1 4 9	Delayed moderate. Delayed very slight. Not appreciable.
4	Adult; just convalescent after sickness giving characteristic symptoms and physical signs of pneumonia; "pneumonia."	Pneumonia.	1 1 1 1	1 4 9 19	Immediate marked. Delayed moderate. Delayed slight. Not appreciable.
5	Adult; continued high fever; enlarged spleen; typhoid bacilli obtained from spleen; "typhoid fever."	Typhoid fever.	1 1 1	1 4 9	Immediate. Delayed incomplete. Delayed very slight.
6	Adult; relapse after four weeks of continuous fever with typhoid symptoms; "relapse after typhoid fever"	Typhoid fever.	1 1 1 1 1	1 10 50 100 200	Marked immediate. Marked immediate. Marked immediate. Delayed moderate. Delayed slight.
7	Adult; seven days continued high fever; typhoid symptoms; two days later an atypical rash; "typhoid fever."	Typhoid fever.	1 1 1 1 1	1 9 49 99 199	Marked immediate. Marked immediate. Marked immediate. Delayed but marked. Delayed moderate.

The Microscopic Examination.

An artificial light is preferable. The use of hanging-drop preparations is unnecessary, as a simple slide and cover-glass is satisfactory. A hanging-drop cell may be extemporized by cementing with marine glue a small brass curtain ring to a slide, and inverting the cover-glass within it, as advised by Stokes.

SERO-DIAGNOSIS OF TYPHOID.

In Table XLVI. I have collected 1,268 cases of supposed typhoid fever in which the clump reaction was tested as above described either with the fluid or dried blood. Of these 1,268

TABLE XLVI.

GIVING THE RESULTS OF THE METHOD OF SERO-DIAGNOSIS IN CASES OF CLINICALLY TYPICAL OR SUSPECTED TYPHOID FEVER, IN CONVALESCENTS OR THOSE WHO HAVE HAD TYPHOID, IN DISEASES OTHER THAN TYPHOID, AND IN HEALTHY SUBJECTS, SHOWING THE NUMBER OF CASES TESTED, THE PERIOD WHEN THE TEST WAS MADE, AND THE REACTION.

Reporter.	Number of cases of typical or suspected typhoid tested.	Day of disease when tested.	Reaction.				Number of convalescents tested.			Number of cases other than typhoid tested.		Number of healthy subjects tested.		Test used.
			Positive		Negative.		Reaction.		Period when tested after convalescence.	Reaction.		Reaction.		
			Decisive.	Partial or feeble.	Decisive or confirmed.	Typhoid fever; no reaction.	Positive.	Negative.		Positive.	Negative.	Positive.	Negative.	
Widal	80	4th to 21st day.	45	..	35	..	6	16	1½ to 9 years.	0	200	0	39	Fluid serum.
Achard	9	7th to 12th day.	3	..	3	3	..	..	....	..	....	..	..	" "
Dieulafoy	2	7th to 12th day.	2	..	..	..	..	..	.. ..	..	No. not stated.	..	..	" "
Chantemesse	11	9th day.	11	..	..	..	..	..	....	0	10	..	..	" "
Rendu	1	11th day.	1	..	..	..	..	..	....	..	....	..	..	" "
Haushalter	39	7th to 12th day.	27	..	12	..	..	..	....	..	....	..	..	" "
Vedel	2	....	1	..	1	..	..	..	....	..	....	..	..	" "
Courmont	13	....	11	..	2	..	..	..	....	..	....	..	..	" "
Catrin	57	4th to 41st day.	36	..	21	..	..	..	......	0	20	..	..	" "
Theolen and Mills	12	....	12	..	..	..	..	..	....	..	....	..	..	" "
Grünbaum	8	10th to 33d day.	8	..	..	..	6	0	4 to 37 years.	*0	4	*0	3	" "
Durham	8	8th to 21st day.	5	..	..	3	4	3	10 days to 6 weeks	..	....	..	..	" "
Delépine	30	8th to 23d day.	24	1	4	1	..	..	....	0	10	..	..	Fluid serum and dried blood.
Greene	16	16th to 38th day.	16	..	..	..	..	..	....	0	19	..	..	Fluid serum.
Johnston	143	48 hours to 3d week.	118	5	14	6	16	1	....	0	35	..	..	Dried blood.
Breuer	45	6th to 14th day of convalescence.	45	..	0	..	1	..	3 months.	..	27	..	..	Fluid serum.
Vanlair and Beco	16	....	9	..	6	1	..	..	....	..	....	..	..	" "
Sabrazès and Hugon	17	2d to 8th day.	13	3	1	..	..	..	....	..	5	..	..	" "

Wright and Smith....	19	....	16	..	3	..	0	14	3 months to 17 years.	0	15	..	..	Fluid serum.
Reed....................	34	5th day and later.	28	..	3	?	0	0	....	1	....	..	..	Dried blood.
Pick	20	3d day and later.	20	0	9	0	0	7	2 to 16 years.	0	8	..	..	Fluid serum and dried blood.
Elsberg	36	4th to 32d day.	36	0	0	0	9	6	1 month to 10 years.	1	146	..	..	Fluid serum.
Le Fevre..............	11	5th day and later.	11	0	0	0	..	..	....	5	109			
Thomas................	28	....	24	..	..	4	2	0	3 to 6 years.	3	13	0	1	Dried blood.
Brannan...............	20	....	18	..	..	2	3	2	2 to 16 months.	1	75	0	15	Dried blood.
Jemma..............	12	....	12	..	..	..	3	..	....	0	15	..	..	Fluid serum.
Stern	16	9th to 16th day.	16	..	..	..	..	..	....	0	4+	..	..	" "
Bartlett	12	....	10	1	1	..	..	2	2 weeks.	0	14	0	4	" "
Gehrmann and Wynkoop.	57	....	48	..	4	5	..	..	....	9	59	..	..	Fluid serum and dried blood.
Coleman	11	8th to 18th day of convalescence.	11	..	..	..	..	..	....	0	6	0	3	Whole blood (fluid).
Biggs and Park..	200	3d to 60th day.	100	..	57	40	5	9	3 months to 14 years.	0	87	..	100+	Fluid serum and dried blood.
Haedke............. ..	22	7th to 42d day.	22	..	..	..	..	..	....	0	20	..	..	Fluid serum.
Craig..................	8	3d, 5th, 8th, and other days.	8	..	..	..	..	..	....	0	12	..	6	Dried blood.
Dempsey	14	....	12	..	2	..	..	..	....	0	4			
Fraenkel	44	2d day to 7th week.	37	..	7	..	21	6	4th day to 7th week.	0	Many.	..	..	Fluid serum.
Ullman and Wöhnert..	19	4th day and later.	19	..	..	..	..	..	....	0	8			
Thiroloix	21	....	21											
Troisier and Sicard....	1	....	1	..	..	..	1	..	....	..	....	..	..	" "
Thoinot	1	....	1	..	..	..	..	..	....	..	....	..	..	" "
Menetrier.............	1	....	1	..	..	..	..	..	....	0	1	..	..	" "
Thiercelin and Lenoble	1	46th day.	1	..	..	..	..	..	....	..	....	..	..	" "
Siredey...............	1	....	1	..	..	..	..	..	....	..	....	..	..	" "
Lemoine..............	1	6th to 11th day.	4	..	6	..	2	..	2d to 6th day.	..	....	..	..	" "
Jez	4	....	4	..	..	..	..	..	....	5	6	4	..	" "
Block	20	8th to 106th day.	11	9	..	..	..	..	....	2	....	..	..	Fluid serum and dried blood.
McWeeney	Several.	....	All.	..	..	..	..	..	....	0	5	..	..	Whole blood.
Cabot..................	116	1st to 69th day.	72	2	39	3	10	2	1 to 30 days.	0	65	0	15	Fluid serum.
Total	1,268	1st to 106th day.	952	21	237	68	89	39	......	27	1,007	4	186	

* The positive reactions obtained by Grünbaum in 15 cases, other than typhoid and in healthy subjects, occurred only when the serum was used in greater concentration than 1 to 10. In mixtures of 1 to 10 the reaction occurred only in typhoid fever.

cases, *952 showed a clump reaction and turned out typhoid, 227 showed no clump and turned out not typhoid. That is, in 1,179, or 93 per cent, of the cases of suspected typhoid, the sero-diagnosis was confirmed by the course of the case.*

Again, out of 1,224 persons who did not have typhoid (190 healthy and 1,034 suffering from various diseases) only 31, or about 2½ per cent, showed any clumping.

How far these may be selected cases, and how true an account of the matter they give, we cannot of course be sure. Biggs and Park, in 77 hospital cases in which they were able to make repeated examinations, never found the reaction wholly absent, although it was only slight in 9. In my own series of 77 hospital and private cases, there were but three in which the reaction was absent, and of these 3, 2 were not tested till convalescence, and the third was tested only once, on the fifth day of illness, death ensuing before another test could be made.

There seems to be no doubt of the fact that the serum reaction is present *in some part of the course* of ninety per cent of all cases of typhoid fever, and absent in ninety per cent or more of all other conditions. But it is also true that it is absent in some part of the course of many cases of typhoid—usually in the earliest or latest days of the fever—and this fact makes it necessary to retest every case in which a negative result has been found, and even in rare cases to make a considerable number of tests before a positive result is obtained.

In 7 of my 77 cases the reaction was absent with the first test but present later on. This leads us to ask: *How early does the reaction appear?*

Few of the many observers who have written on this point have discussed how the beginning of the disease is settled and what they mean, *e.g.*, by the "fifth day of the disease." It might be dated from the first day of malaise and indisposition, from the nose-bleed or the beginning of headache, or from the time of going to bed.

Allowing for such serious uncertainties as this, we find that while the majority of observers record the sixth to eighth day as the earliest on which the reaction appears, there are quite a number of cases mentioned in which it was seen on the fourth or fifth day; four articles (Fraenkel's, Pick's, Craig's, Biggs and

Park's) record reactions on the third day, and two (Fraenkel's, Sabrazé and Hugon's) on the second day.

As above mentioned, we have no way of knowing what the "second day" means in these cases.

In my own observations I have called *the first day in bed the first day of the disease* (though I am aware that many patients are sick some time before taking to bed), because it was the only date that could be definitely fixed in all cases. With this nomenclature I have found the reaction present on the first day in two cases and on the second in three cases.

Counting from the first day on which the patient felt sick *in any way*, the *fifth day* is the earliest reaction day in my series. In these figures we have always to remember that in no case was the blood tested at all previous to the day on which the positive test occurred, so that their meaning is: *In some cases* (what proportion of all is unknown) *the serum reaction occurs at least as soon as the fifth day of malaise or the first day in bed, and perhaps sooner.*

Observations as to *how often* we find reaction on these early days are confined, so far as I know, to those of Biggs and Park. Out of 19 cases examined between the "third and seventh day," 12 cases, or 63 per cent, reacted positively.

In my series, out of 20 cases examined between the first and seventh day of taking to bed, 17, or 85 per cent, reacted positively. In 2 of my cases the serum reaction was present five days before the appearance of rose spots or splenic enlargement. Once the serum reaction anticipated the diazo by two days, and in 2 cases it was positive when the diazo was absent throughout the disease.

Experiments on animals show that the clump reaction appears in the blood on the third to eighth day after inoculation with dead typhoid bacilli.

How late in the disease does the reaction last? The majority of observations agree that in mild cases the reaction may die out even before the end of the fever. On the other hand, Block has followed a case for one hundred and six days from the beginning and constantly found the clumping to occur, and Widal found it still present after one year in 3 out of 22 cases in which he tried it. These 3 subjects had had very severe cases of typhoid three, seven, and nine years previously. These figures indicate the limits. Biggs and Park found the reaction more constant in

the fourth week than at any other time—76 per cent of his cases tested between the thirtieth and sixtieth days still showed the reaction, and 5 of 8 cases still reacted after three to four months.

The reaction almost always persists in relapses, even to a second or third relapse, and occasionally it is present *only in relapse and not in the original attack at all.* Biggs and Park record a case in which the diagnosis was proved during the original attack by puncture of the spleen, which showed a pure culture of Eberth's bacilli, yet no serum reaction was present until the second day of the relapse. I have observed two similar cases. In one of Elsberg's cases the total duration of the clumping power in the blood was only eight days; in another only twelve days.

The continuance of the reaction after the fall of the temperature is no indication (as some have supposed) that relapse is coming, for in many such cases no relapse follows.

The Intensity of the Reaction.

Widal and others have studied the intensity of the reaction at different periods of the disease, judging by the amount of dilution which could be practised without destroying the power of a given serum.

Examples of this have already been given in the table on page 363. The majority of typhoids in the second and third week yield serum which will clump Eberth's bacilli when diluted 1:40 and many cases will do so even at 1:100. Strangely enough, some typhoid sera clump better when diluted 1:16 or more than when undiluted. This has been repeatedly noted by Grünbaum.

Widal and Sicard record clumping with a dilution of 1:12,000 and 1:1,800 and consider that in the active stages of the disease a dilution of 1:60 or 1:80 does not usually present the reaction, while in convalescence the power of the serum falls off gradually and is not always present even at 1:10.

Biggs and Park find one-half their typhoid cases furnish serum with the power to clump in 1:40 dilution by the end of the first week, and have occasionally noted the reaction even with a dilution of 1:200.

Jemma found the reaction most intense at the acme of the

fever and greater during the evening exacerbation of fever than in the morning.

Effects of the Sera of Other Diseases.

Negative results are reported in the following list of diseases experimented on as controls: Pneumonia, typhus, Malta fever, tuberculosis in its various forms, including miliary tuberculosis, tubercular meningitis, pneumococcus meningitis (purulent) and epidemic cerebro-spinal meningitis, diphtheria, influenza, ulcerative endocarditis, erysipelas, puerperal septicæmia, gonorrhœal septicæmia, measles and scarlet fever, tonsilitis, acute articular rheumatism, malaria, leprosy, syphilis, bronchitis, pleurisy with effusion, acute and chronic nephritis, mumps, otitis media, catarrhal jaundice, sciatica, acromegalia, hysterical vomiting, Graves' disease, gangrene of the lung, appendicitis, abscess and cirrhosis of the liver, acute febrile gastro-enteritis ("embarras gastrique"), cancer of the various organs, alveolar abscess with fever, osteomyelitis, bubo with fever, arthritis deformans, chronic laryngitis, intestinal obstruction, general peritonitis, leukæmia, Hodgkin's disease, pernicious anæmia, diarrhœa, chronic gastritis, gallstone colic with fever, dysentery, acute mania, stuporous melancholia, synovitis, neurasthenia, varicose veins, orchitis, suppurative thyroiditis, perinephritis, cystitis, pericarditis, empyema, brain abscess, valvular heart disease, diabetes, gas poisoning, alcoholism, and eclampsia.

The important diseases of this list, such as pneumonia, tuberculosis, meningitis, and typhus, have been tried many times. Biggs and Park got a positive result in one case said to be typhus. There is a chance of mistaken diagnosis here.

Positive Results of the Sera of Other Diseases with Typhoid Bacilli.

Many of the supposed contradictions of the law, that the *typhoid bacilli are clumped within one-half hour only by typhoid serum when a dilution of one part of serum to ten or more of culture is used*, are due to faulty technique. Such are probably the cases reported by Ferrand and Theoari (septicæmia), Villies and Battle (malaria), Gehrmann and Wynkoop (pneumonia, bronchitis, pleurisy), and Stern (otitis media).

On the other hand there are a few cases reported by careful observers in which a genuine clumping of typhoid bacilli has been caused by the sera of other diseases, viz.: Pernicious malaria, comatose, one case (Block); diabetic coma, one case (Block); jaundice, one case (Catrin); tubercular meningitis, one case (Jez).

A case of malaria, reported by Catrin, with positive reaction of the serum on typhoid bacilli, was in a subject who had had typhoid five years before. In view of Widal's and Fraenkel's results, this cannot be counted an exception to the general law. The same is true of Grünbaum's much-quoted cases, which he reported *not* as exceptions but to emphasize the necessity of proper dilution. Using a proportion of 1:1 instead of 1:10, he got clumping of typhoid bacilli with the sera of jaundice (two cases), meningitis and bronchitis (one case each).

The cases reported by Johnson, Brannan, Thomas, Reed, and other observers, in which the dried blood of healthy persons and persons with various diseases other than typhoid has clumped typhoid bacilli, are probably owing to the uncertainties connected with that method of procedure.

In most cases in which the fluid serum was also tried it gave no reaction.

The discovery that the bacillus of psittacosis and the "bacillus enteritidis" of Gärtner are somewhat sensitive to the action of typhoid serum (see page 372) has led to the fear that infections due to those bacilli might be mistaken for typhoid, but this is wholly an assumption, as in the few cases of these infections which have been studied the serum has not affected typhoid bacilli.

Further, it is only by a concentrated artificial typhoid serum that the bacillus of Gärtner is clumped, and the clumping of the psittacosis bacillus is quite different from that of the typhoid bacillus, the clumps of the former being very small and few; with the twenty-four-hour method no precipitate forms.

Summary of Negative Results.

Out of over one thousand cases of various diseases not typhoid, but four have been proved to clump typhoid bacilli with proper technique. It is quite possible that further im-

provements in technique may enable us to prevent even this very small error.

EFFECTS OF TYPHOID SERUM ON OTHER BACILLI.

(a) *On the Bacillus Coli Communis.*

Any blood serum mixed 1:10 with a bouillon culture of colon bacilli may cause the formation of *small* clumps without considerable loss of motility. The effect of typhoid serum does not differ from that of other sera, and the clumps which it forms are much smaller and looser than those seen in the typical typhoid clump reaction. Different cultures of colon bacilli differ a good deal in their susceptibility to typhoid serum, and Vanlair and Beco consider that no difference can be made out in certain cases between its effects on typhoid bacilli or on colon bacilli. The majority of observers, however, find a decided difference, especially with the twenty-four-hour method. *Undiluted* typhoid serum acts more strongly on colon than on typhoid bacilli, according to Grünbaum.

Biggs and Park found that "a number of varieties of motile bacilli other than typhoid bacilli are clumped by the serum of persons suffering from typhoid fever, even when the serum is used in quite high dilutions."

Rodet noted that only a very slight effect is produced by typhoid serum on colon bacilli until a dilution of one part of serum to two of culture is reached.

Fraenkel tested a large number of colon cultures without getting any decided effect from the addition of typhoid serum.

Courmont found that some cultures of the colon bacillus are clumped by typhoid serum.

Widal saw no difference between the effect of typhoid serum and that of other sera on colon bacilli, but Vedel thinks that young cultures are better clumped by typhoid serum than by other sera.

Johnson, who studied a large number of cases, says: "A complete colon reaction we have found to be exceptional in ordinary typhoid, and its presence would indicate a condition of coli intoxication," which may be held to sum up the discussion up to the present time.

(b) *On the Bacillus Enteritidis (Gärtner).*

Grüber and Durham, using powerful artificial sera from animals immunized against Eberth's bacillus, were able to obtain a clumping of Gärtner's organisms. No experiments with human serum are recorded.

(c) *On the Bacillus of Psittacosis.*

Psittacosis is a disease affecting parrots and occasionally transferred by them to human beings. A bacillus has been found by Nocard in the marrow of the parrot's wing-bones which is considered the cause. Typhoid serum has an effect on bouillon cultures of this bacillus, which is to be distinguished quantitatively from the clumping of typhoid bacilli by typhoid serum; the heaps of psittacosis bacilli are much fewer and smaller, and in the twenty-four-hour method the turbidity of the cultures does not disappear.

(d) *The Klebs-Loeffler Bacillus and Pus Cocci.*

Courmont finds that typhoid serum clumps Klebs-Loeffler bacilli and staphylococci, but is without effect on the streptococcus and the bacillus pyocyaneus.

Summary of Clinical Evidence on the Sero-Diagnosis of Typhoid Fever.

The blood of over ninety per cent of all cases of typhoid shows a clumping power in some part of their course, but in at least half the cases this does not appear until the second week of the disease, while in a small number of cases it first appears in relapse. The clumping power may disappear before the defervescence and may be present only eight days in all; as a rule it persists from the sixth or eighth day until convalescence is established.

In diseases other than typhoid a clump reaction is very rarely to be obtained, provided a dilution of at least 1:10 is used with a time limit of one-half hour. There is no one disease in which clumping is especially apt to occur.

Clinically the reaction is of considerable value, especially when the diagnosis is in doubt after the first week of the disease.

Sero-Diagnosis of Diseases Other than Typhoid.

1. *Cholera.*

Grüber and Durham first showed that human cholera serum would clump cholera vibrios, following the researches of Pfeiffer *in vivo* by demonstrating a similar reaction *in vitro.*

Achard and Bensaude have applied this to the actual diagnosis of cholera in man with considerable success.

2. *Pyocyaneus Infections.*

The bacillus pyocyaneus has been shown to be in all probability the cause of certain cases of dysentery, broncho-pneumonia, otitis media, nephritis, pericarditis, cystitis, and of a hemorrhagic septicæmia with enteritis in the new-born.

Roger and Charin found in 1889 that the bacillus pyocyaneus is serum of animals immunized against this bacillus. Durham repeated these observations in 1895 and confirmed them.

Here we have the clinical infection and laboratory clump-reaction experiments, but so far as I am aware no one has yet brought the two together or tried the serum of patients with pyocyaneus infections on cultures of the bacillus.

3. *Diphtheria.*

Widal reports no success in attempts at the sero-diagnosis of diphtheria, and Fraenkel has not been more successful. Nicolas and Charrin found that, although no true serum reaction could be obtained in diphtheria previous to antitoxin treatment, the injection of antitoxin produces in the patient's serum a decided clumping power over the Klebs-Loeffler bacilli within twenty-four hours of the time of injection. This is especially marked in the twenty-four-hour method, using the *nascent* bacilli, as described on page 356. The serum retains its clumping power for about two weeks after the injection of antitoxin, and then gradually loses it. Outside the body the diphtheria antitoxin easily clumps Klebs-Loeffler bacilli.

4. *Pneumococcus Infections.*

Washburn in 1895 noticed that pneumococci, when mixed with artificial antipneumococcus serum and left twenty-four hours at 37°C, were clumped in masses at the bottom of the tube, leaving

the upper portions of the liquid clear. In other words he got a typical twenty-four-hour clump reaction, using a powerful artificial serum. The same fact had previously been observed by Metchnikoff in 1891 and by Issaef in 1892, and has been recently confirmed by Mosny.

Widal has been entirely unsuccessful in finding any clumping with the serum of pneumonia patients, and Block finds the clumping of pneumococci very slow and unsatisfactory.

5. *Colon-Bacillus Infections.*

In view of the frequent association of this bacillus with disease, especially with the cystitis of young girls, it is important that the possibility of a sero-diagnosis of colon-bacillus infections should be studied, but as yet very little has been done in this direction.

Grüber and Durham showed that serum from animals artificially immunized against the colon bacillus would clump that bacillus strongly, but Widal's experiments with supposed cases of colon-bacillus infection did not show any decided reaction, nor did the serum of typhoids which showed post mortem a secondary colon-bacillus infection react during life on cultures of this bacillus.

On the other hand Vedel reports a case with the clinical aspect of typhoid yet with no serum reaction, in which there was a marked reaction with the colon bacillus. In this case defervescence occurred on the tenth day, and Vedel is inclined to believe that some cases hitherto considered as mild or abortive typhoid can be shown by the serum reaction on the colon bacillus to be due to that organism.

Johnson has been "struck by the large proportion of positive colon reactions obtained in cases having 'step-ladder' temperature and other symptoms strongly resembling typhoid but without the typhoid-serum reaction." He thinks that "under these circumstances the colon reaction may have a real diagnostic importance, and indicates that the colon infection, whether occurring alone or as a secondary complication of typhoid, may be playing an important part in the production of the patient's condition. The whole question of associated colon infection deserves further study."

6. *Malta Fever.*

Wright and Smith tested the serum of 15 cases of Malta fever with the *micrococcus melitensis* of Bruce, and found a strong clump reaction to occur (1:50 in most cases). On the typhoid bacillus the serum of these cases had no action. Sixteen cases of typhoid showed no reaction with Bruce's organism. The evidence in favor of this organism as the cause of Malta fever is strengthened by these facts.

7. *Peripneumonia of Cattle and Hog Cholera.*

Arloing finds that the serum and other body fluids of cattle suffering from peripneumonia have a marked clumping power on the pneumobacillus bovis.

Dawson has had similar positive results working with the bacillus of hog cholera. Hog-cholera serum had no effect on the typhoid or colon bacillus.

8. *Proteus Infections.*

Infections with the proteus vulgaris or proteus mirabilis have been considered causative in cases of mastoid abscess, meningitis, and Potts' disease. When found by culture at autopsies the question often arises whether they have wandered in after or at the time of death, or whether they were really concerned in the etiology of the case. The investigations of Achard and Lannelongue appear to give us the means of answering this question. They found that cultures of the two species of proteus above mentioned were markedly clumped by the serum of animals rendered immune to them by inoculations. This power persists after death and even in putrefaction, and if present at any given autopsy proves that the infection did not take place during the last two days of life, since it takes *at least three days* to bring the clumping power into the serum by artificial inoculation.

9. *Oidium Albicans.*

Roger showed that the oidium was well clumped by the serum of animals immunized against it, and these observations have been confirmed by Charrin and Ostrowsky. No experiments with human thrush have as yet been reported.

10. *Miscellaneous Reports on Other Infections.*

(*a*) Grünbaum (*Lancet*, February 13th, 1897) states that a "non-motile diplococcus" from a case of *scarlet fever* was clumped by the serum of another case of scarlet fever.

(*b*) Delépine (*Medical Chronicle*, October, 1896) refers to successful experiments with the *tetanus bacilli*—its antitoxin having a decided clumping action upon it.

(*c*) Durham (*Lancet, loc. cit.*) speaks of the present antistreptococcus serum (Marmorek's) as having strong clumping power on *streptococci*.

(*d*) Gilbert and Fournier (*Compt. rend. de la soc. de biol.*, December 25th, 1896) mention two cases of human psittacosis whose serum clumped well the bacilli obtained from another human case as well as those taken from parrots. Clumping was present on the fourth and fifteenth days respectively.

THE NATURE OF THE CLUMPING PROCESS AND OF THE CLUMPING SUBSTANCE.

1. The question as to whether or not the clumping reaction in typhoid is "*specific*" has been much debated. Most observers are now agreed that whatever right it has to the term "*specific*" rests on the fact that typhoid serum will clump in greater dilution than that of any other known disease. It is a *quantitative*, not a *qualitative* affair.

2. Discussion has also raged round the question whether the clump reaction expresses *immunity*, or whether, as Widal has steadily maintained, it is a reaction of *infection*.

Certainly we must modify our usual ideas of immunity if it is expressed by a reaction which can appear as soon as the symptoms do, disappears frequently during or before convalescence, and is present just before relapse. Further, Achard found that the serum which had lost its clumping power on the tenth day after defervescence conferred as great an immunity on animals as the serum of the same patient taken during the height of the disease and of the clumping power of the serum. Bacilli when not clumped are not destroyed and will grow freely if replanted; serum will clump after being heated to 59° C.; so that

its power is evidently not bactericidal, and its action on dead bacilli would be hard to explain as—bactericidal!

These considerations seem to the majority of observers conclusive evidence against the propriety of the use of the word immunity. On the other hand, it is strange that a reaction of *infection* should be intense in mild cases and absent in very severe ones, as has occurred.

The clumping powers of the serum are evidently distinct both from its natural and non-specific bactericidal power (Buchner's "alexins") and from the specific immunity against a given disease which may be artificially conferred, as by diphtheria antitoxin. That various organisms other than typhoid are clumped and attenuated by their appropriate antitoxins (diphtheria, etc., see above), does not prove that the preventive and clumping powers are identical in typhoid, but only shows that in those particular preventive sera the power to clump their appropriate bacilli is present as well, perhaps owing to peculiarities in horse's-blood serum.

3. The loss of motility in connection with the clumping is probably a by-action of the serum, perhaps an expression of its natural bactericidal power, as various other sera will check the motility of typhoid bacilli, and dead, motionless bacilli clump as well as those that are motile (see page 360).

Nature of the Clumping Substance.

Widal and Sicard have shown that in typhoid serum or other actively clumping fluids (see page 351) the clumping power resides in the *globulin* and *fibrinogen*, and not at all in the serum albumin. This globulin of typhoid blood is identical chemically with the globulin of normal blood (Devoto).

In milk it is the casein (lacto-globulin) that possesses the clumping power.

Filtration through porcelain destroys or greatly attenuates the clumping power. It seems not to pass the placenta in human infections, as the observations of Etienne, Apert, and Charrin have failed to find it in the fluid of infants born of typhoid mothers. On the other hand, Widal and Sicard *did* find it in the litter of an immunized rabbit. It will pass through parchment.

A temperature of 66° C. does not destroy it, and even after ten minutes at 75°C. it is not wholly gone; 80°C. wholly destroys it.

Achard and Bensaude made a set of careful studies to ascertain whether the leucocytes were responsible for the clumping action of the serum through their secretory power. (The fact that blister fluid free from leucocytes clumps well, excludes any dependence of the reaction on their actual presence.) They separated and kept alive the leucocytes of typhoid blood whose serum clumped strongly. These were washed with artificial serum until the filtrate gave no clump reaction; a liquid was then squeezed out of them by strong pressure. This liquid gave no clump reaction, yet the leucocytes were still alive enough to take up carmine granules.

Two more facts relative to the clumping power must be added, though they confuse rather than clarify our ideas.

1. The serum of normal horses has strong clumping power on typhoid, cholera tetanus, and colon bacilli.

2. Chrysoidin has been shown by Blachstein to possess the power to clump the vibrio of Asiatic cholera, though it has no effect on allied vibrios nor on other bacilli. Substances chemically very close to chrysoidin are inert in relation to the cholera vibrio.

SERO-PROGNOSIS.

It is agreed by all observers that in a very general way severe cases have more marked reactions than mild ones, but beyond this, in the opinion of the best judges, we cannot yet go.

Widal, Fraenkel, Biggs and Park, and Johnson have attempted no sero-prognosis, and my own observations are entirely in accord with this. The reaction may be strong in mild cases and feeble or absent in fatal ones.

Certain writers, however, especially Breuer, Courmont, Catrin, and Ullmann and Wöhnert, have thought the reaction of prognostic value, an intense and early reaction seeming to them of evil omen. Further evidence on this point is much needed.

[For bibliography, see page 428.]

APPENDIX.

NEUSSER'S PERINUCLEAR BASOPHILIC GRANULES.

Using the following modification of Ehrlich's tricolor mixture, Neusser[1] believes that he can bring out certain characteristics in the leucocytes of value in diagnosis and prognosis.

Saturated aqueous solution of	Acid fuchsin	50 c.c.
	Orange G	70 "
	Methyl green	80 "
Distilled water		150 "
Absolute alcohol		80 "
Glycerin		20 "

Cover slips stained with this mixture show in certain diseases (*e.g.*, gout, leukæmia) a grouping of dark blue-stained granules around the nuclei of the mononuclear leucocytes and over and around the nuclei of polymorphonuclear leucocytes. These granules appear to take up only the basic part of the tri-color mixture.

For Neusser's conclusions regarding the meaning of these granules, the reader is referred to pages 222 and 276.

[1] Wien. klin. Woch., 1894, No. 39.

BIBLIOGRAPHY.

It has seemed to me best to give a list of the books and articles which I have found most useful, classing those found less valuable with the general bibliography.

Text-Books.

1. Hayem: "Du Sang," Paris, 1889, 8vo, 1035 pages (French). This valuable book is the largest that I know of on the subject, and contains a mine of information on the morphology of the blood in health and disease, mostly from the author's own experience, literature being but little referred to. It contains a comparative anatomy of the blood and a long account of blood development. Unfortunately, it is dominated throughout by a theory of blood formation which has never gained acceptance by any other authority. It is very full on the subject of fibrin formation and of chlorosis. The illustrations are excellent.

2. v. Limbeck: "Grundriss ein. klin. Pathologie des Blutes," Jena, 1896, 8vo, 383 pages (Fischer). The second edition of this book, which appeared in February, 1896, is more than twice the size of the first edition (1892)—a fact illustrating the rapidity of the subject's growth. It is on the whole the best general text-book known to me, being equally full on all parts of the subject, including, for example, technique (which Grawitz omits) and of the chemistry the blood, which is at present the author's special interest and on which Hayem is meagre. The illustrations are poor and the type is trying to the eyes. The writer shows little personal experience with the morphology and microchemistry of the blood, and this is the weakest side of the book. A large part of the book is concerned with the physiology of the blood.

3. Grawitz: "Klinische Pathologie des Blutes," Berlin, 1895, 8vo, 333 pages (Enslin). Issued in April, 1896. This book is the latest known to me. It is largely devoted to the matter indicated by the title and contains no account of blood technique, and only thirty pages on the normal anatomy and physiology of the blood, while two hundred and seventy concern the blood in disease. The arrangement of the book is very clear and helpful. The author's main interests are in the estimation of the dried residue of the blood in various diseased conditions and in the bacteriology of the blood, so that the book is specially full on these topics. The illustrations are poor. Type and paper are excellent.

4. Schmaltz: "Pathologie des Blutes und die Blutkrankheiten," Leipzig, 1896, 16mo, 268 pages (Naumann). A much smaller book than either of the others and including the symptoms, pathology, and treatment of blood diseases, as well as a pathology of the blood itself. Specific gravity of the blood is a point of special interest with the author. There are no illustrations. The book is excellent as far as it goes, well arranged, and clear.

These are the best text-books known to me on the whole subject. None of them have been translated.

Text-Book Articles on Blood Diseases.

1. Osler, in the "American Text-book of the Theory and Practice of Medicine," vol. ii. (Philadelphia, 1894, Saunders), writes a fifty-page article on "Diseases of the Blood," which is the standard work on the subject in English. It covers, of course, only the blood diseases proper without much account of the blood in other conditions.

2. Stengel's article in vol. vii. of the "Twentieth Century Practice of Medicine" is excellent.

3. The article "The Blood in Infancy," in Rotch's Pædiatrics, covers this branch of the subject very thoroughly and is up to date (1895).

These are the best articles in English that I know of.

4. The article on "La Pathologie du Sang," by Gilbert, in the five-volume "Traité de Médecine" edited by Charcot, Bouchard, and Brissaud, Paris, 1892 (Masson), is inferior to those last mentioned and is mostly an echo of Hayem's work above referred to. Theories long exploded (*e.g.*, that eosinophiles are pathognomonic of leukæmia) receive the author's sanction. The article is one hundred large octavo pages long and is intended to cover the whole subject.

5. Griffith's eighty-page article in Keating's "Cyclopædia of the Diseases of Children," vol. iii., p. 755 (Philadelphia, 1890, Lippincott), is now a good deal out of date.

6. The articles on blood diseases in the latest editions of the text-books of Osler, Strümpell, Da Costa, Flint, and Fagg, contain relatively little about the blood itself.

Treatises on Special Portions of the Subject.

1. Reinert's "Die Zählung der Blutkörperchen" Leipzig, 1891 (Vogel), 246 pages, is an admirable account of the avoidable and unavoidable errors in blood examination, and the best methods of reducing error to a minimum. A number of careful examinations of the blood in health and in various diseases are also given; and an outline of the scope of blood diagnosis closes the book.

2. Rieder's "Beiträge zur Kenntniss der Leukocytosis," Leipzig, 1892 (Vogel), 220 pages, is an admirable work in all respects, although

now considerably out of date. It shows, as very few of the foregoing treatises do, a practical acquaintance, on the author's part, with the details of blood morphology and microchemistry. A very large number of blood counts in many diseases is recorded.

3. Löwitt's "Studien zur Physiol. und Pathol. des Blutes u. der Lymphe" (Jena, 1892 [Fischer], 8vo, 138 pages) is mostly concerned with experiments on animals and intended to throw light on the theory of leucocytosis. The conclusions of the book have not been generally adopted, though its facts have been mostly verified.

4. Thayer and Hewetson's book, on the "Malarial Fevers of Baltimore," leaves nothing more to be desired in that direction. It is two hundred and fifteen pages long, published by the Johns Hopkins press of Baltimore in 1895. It contains a summary of the literature of the subject, an analysis of six hundred and sixteen new cases, and some admirable colored plates. It is a model of its kind in every respect, and an ideal for others to aim for.

5. Ehrlich's "Farbenanalytische Untersuchungen" (Berlin, 1891 [Hirschwald], 137 pages) contains nine short essays by Ehrlich and three by his pupils. Considering the reputation of the writer they are at the present day rather disappointing reading and contain little that is not better expressed elsewhere.

6. Under a somewhat different heading come the sections on the examination of the blood in v. Jaksch's "Clinical Diagnosis" (English translation, London, 1893, Griffen & Co.), a seventy-five-page article containing many inaccuracies; and Lenharz: "Microscopie und Chemie am Krankenbett" (Berlin, 1896, Springer), a fifty-page article.

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